

Review article

Shivaji, Uday N.; Sharratt, Caroline L.; Thomas, Tom; Smith, Samuel C. L.; Iacucci, Marietta; Moran, Gordon W.; Ghosh, Subrata; Bhala, Neeraj

DOI:

[10.1111/apt.15097](https://doi.org/10.1111/apt.15097)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Shivaji, UN, Sharratt, CL, Thomas, T, Smith, SCL, Iacucci, M, Moran, GW, Ghosh, S & Bhala, N 2019, 'Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease', *Alimentary Pharmacology & Therapeutics*, vol. 49, no. 6, pp. 664-680. <https://doi.org/10.1111/apt.15097>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is the peer reviewed version of the following article: Shivaji, UN, Sharratt, CL, Thomas, T, et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2019; 49: 664– 680. , which has been published in final form at <https://doi.org/10.1111/apt.15097>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

**Review article: Managing the Adverse Events Caused by
Biologics Therapy in Inflammatory Bowel Disease**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID	APT-1143-2018.R3
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Shivaji, Uday; NIHR Birmingham Biomedical Research Centre; University of Birmingham, Institute of Immunology and Immunotherapy Sharratt, Caroline; Nottingham Digestive Diseases Centre Thomas, Tom; University Hospitals Birmingham NHS Foundation Trust, Gastroenterology Smith, Samuel; Institute of Translational Medicine, University of Birmingham Iacucci, Marietta; NIHR Birmingham Biomedical Research Centre, Institute of Immunology and Immunotherapy Moran, Gordon; The University of Nottingham, Nottingham Digestive Diseases Biomedical Research Unit Ghosh, Subrata; NIHR Birmingham Biomedical Research Centre, Institute of Immunology and Immunotherapy Bhala, Neeraj; University Hospitals Birmingham NHS Foundation Trust, Gastroenterology; University of Birmingham
Keywords:	Crohn's disease < Disease-based, Inflammatory bowel disease < Disease-based, Ulcerative colitis < Disease-based, Biologics (IBD) < Topics, Immunosuppression < Topics

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

To,
Prof Roy Pounder and Dr. Nicholas Kennedy,
Editors,
Alimentary Pharmacology and Therapeutics

Dear Prof Pounder and Dr. Kennedy,
Thank you for your valuable comments on the review article we submitted with reference number APT-1143-2018. We also would like to thank the reviewers.
We have now changed the title of the manuscript as per your suggestion and resubmitted a tracked and clean copy.
The title now reads- Managing the Adverse Events Caused by Anti-TNF Therapy in Inflammatory Bowel Disease
We hope this is to your satisfaction.
Thank you
Yours sincerely
Uday Shivaji, Neeraj Bhala and Prof Subrata Ghosh

**Review article: Managing the Adverse Events Caused by Anti-TNF Therapy Biologics
Therapy in Inflammatory Bowel Disease**

Shivaji UN^{1,2}, Sharratt CL^{5,6}, Thomas T⁴, Smith SCL³, Iacucci, M^{1,3}, Moran GW^{5,6}, Ghosh S^{1,3}, Bhala N^{4,7}

¹ National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre

² Institute of Immunology and Immunotherapy, University of Birmingham (UK)

³ Institute of Translational Medicine, Birmingham, UK

⁴ Department of Gastroenterology, University Hospitals Birmingham, UK

⁵ National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre

⁶ Nottingham Digestive Diseases Centre, Nottingham University Hospitals

⁷University of Birmingham, Birmingham, UK

Keywords: Crohn's, Ulcerative Colitis, Infliximab, Adalimumab, Golimumab, Biologics, Anti-TNF α Complications, Adverse events

Corresponding Author:

Prof. Subrata Ghosh

Professor of Medicine

Director, Institute of Translational Medicine

University of Birmingham, Edgbaston. B15 2TH

United Kingdom

Office Phone: 0121 371 8026

Email: GhoshS@adf.bham.ac.uk

- 1 Shivaji,UN- literature search, evidence procurement, writing and editing manuscript, revision and approval
- 2 Sharratt,CL- literature search, evidence procurement, writing manuscript, revision and approval
- 3
- 4 Thomas,T- literature search and writing sections of manuscript, approval
- 5
- 6 Smith,SCL- editing manuscript, revision, approval
- 7
- 8 Iacucci,M- revision, critical review of manuscript, approval
- 9
- 10 Moran,GW- literature search, critical review of manuscript, revision, approval
- 11 Ghosh,S- Plan of this review, critical review of manuscript, revision, overall supervision and final approval
- 12
- 13 Bhala,N- critical review of manuscript, revision, overall supervision and final approval
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

For Peer Review

STRUCTURED SUMMARY

Background

Biological therapy is currently widely used to treat inflammatory bowel disease (IBD). Infliximab, adalimumab and golimumab are currently licensed anti-TNF therapies. Biosimilar anti-TNF monoclonal antibodies are increasingly used. Anti-TNF therapies are most widely used and their adverse effects are best characterised, which may cause significant morbidity and mortality in a small proportion of exposed patients. Gastroenterologists need to understand the mechanism for these effects, recognise these swiftly and manage such events appropriately.

Aim

This review aims to cover the range of potential adverse reactions as a result of biologic therapy and specifically management of these events.

Methods

A Medline and Pubmed search was undertaken. Search terms included were “anti-TNF”, “infliximab” or “adalimumab” or “golimumab” combined with the keywords “ulcerative colitis” or “Crohn’s disease” or “inflammatory bowel disease” and then narrowed to articles containing the keywords “complications”, “side effects” or “adverse events” or “safety profile”. International guidelines were also reviewed where relevant.

Results

Adverse events discussed in this review include infusion reactions, blood disorders and infections (including bacterial, viral, fungal and opportunistic infections) as well as autoimmune, dermatological disorders, cardiac and neurological conditions. Malignancies including solid organ, haematological, and those linked to viral disease are discussed.

Conclusions

Anti-TNF therapy has wide-ranging effects on the immune system resulting in a spectrum of potential adverse events in a small proportion of patients. Research advances are improving understanding, recognition and management of these adverse events.

INTRODUCTION

The use of biologics is currently approved for moderate-to-severe Crohn’s disease (CD) and moderate to severe ulcerative colitis (UC)¹⁻⁹. Infliximab, adalimumab and golimumab are antibodies to tumour necrosis factor- α (TNF α). These drugs work on a common pathway of blocking TNF α , a pro-inflammatory cytokine closely linked to acute phase reaction and systemic inflammation, thereby reducing the degree of damage to tissues. These have been developed using different techniques therefore conferring different degrees of immunogenicity. [Infliximab (human-chimeric), adalimumab (fully human), golimumab (fully human), certolizumab (recombinant pegylated humanised Fab’ fragment)].

These medications have transformed medical treatment options for inflammatory bowel disease (IBD) in recent years and are prescribed in increasing numbers. As there are less golimumab exposed patients than the other two anti-TNF monoclonal antibodies, less adverse effects have been reported but generally most adverse effects are class effects. Clinicians need to be aware of & recognise adverse events (AE/AEs) that may result from the use of these drugs and also have clear management strategies in different scenarios. This comprehensive review summarises a range of possible AEs providing evidence based guidance where available and pragmatic guidance for areas where evidence is lacking.

AIMS AND METHODS:

A MEDLINE and PUBMED search was undertaken by (U.S, C.L) for articles pertaining to adverse effects of anti-TNF therapy in IBD. After an initial title screen, all relevant articles were examined in full. The main aim of the review is to focus on management of adverse events caused by anti-TNF therapy. For clarity, these AEs are discussed in categories as per systems, alongside recommended course of action including any further investigations or management. Where relevant, this manuscript also refers to international guidelines.

Non-infectious complications and management strategies

Hypersensitivity reactions

Hypersensitivity reactions vary widely in presentation, ranging from acute infusion reactions to delayed hypersensitivity.

- Type I acute hypersensitivity reactions (IgE mediated) present as anaphylaxis
- Type II are cytotoxic; complement-mediated
- Type III are immune-complex related presenting as serum sickness
- Type IV are cell-mediated delayed hypersensitivity; mediated by T lymphocytes

Acute infusion reactions (IR) are defined as those which occur during or within 24 hours of the infusion. The symptoms vary and reactions can range from mild (flushing, dizziness, headache, itching, rash) to severe (anaphylactic-like)². Acute infusion reactions are relatively common, estimated to occur in up to 5% of infusions, with less than 1% of all infusions resulting in a severe reaction³.

Patients with antibodies to infliximab are at an increased risk of infusion reactions⁴ and case reports suggest hypersensitivity to adalimumab are also associated with adalimumab antibodies⁵. A review by the Food and Drug Administration (FDA) reported that injection site reactions were more common with adalimumab⁶ with higher reporting odds ratio(ROR) in the 20-29y age group (ROR=16.18). The ROR was seen to reduce with increasing age⁶. Injection site reactions to golimumab in the PURSUIT

study were low at 3.4% with no reported anaphylaxis or delayed hypersensitivity to 6 weeks⁷. Delayed reactions (24 hours to 14 days) presenting with arthralgia, myalgia, fever, fatigue and rash are much rarer (<1%)³. The pathophysiology of immunologic features are not completely understood⁸.

Management

The management of IRs is generally similar regardless of which agent has caused it. Typically, symptoms improve substantially or resolve completely after infusion rate adjustments and treatment with paracetamol, antihistamines or corticosteroids are provided. Evidence to support the use of premedication with corticosteroids or antihistamines is limited, with patients still experiencing infusion reactions despite pre-medication⁹ and therefore should be considered on an individual basis. Injection site pain due to adalimumab can be reduced by using low volume formulations which are free from citrate buffers, with no change in efficacy¹⁰.

In severe acute reactions, it is recommended that infusion is stopped and focus should be on maintaining airway, circulation as per standard anaphylaxis guidelines¹¹. (Table 1) Delayed infusion reactions are typically managed by antihistamines, paracetamol and corticosteroids. A systematic review looked at management of infusion reactions and presented useful algorithms to manage mild, moderate and severe reactions¹². These algorithms are simple, and a pragmatic tool to use for the vast majority of reactions seen in clinical practice¹². After a hypersensitivity reaction, it is pragmatic to obtain therapeutic drug levels and anti-drug antibody levels.

Table 1- Hypersensitivity reactions to anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Type 1 Hypersensitivity This is more common when antibody titres are high. Incidence is higher during re-introduction of drugs	<ul style="list-style-type: none"> Clinical diagnosis Serum mast cell tryptase Detection of antibodies on serum analysis where available 	<ol style="list-style-type: none"> Mild reactions: Slow infusion rates Consider hydrocortisone injections as a pre-administration medication Anaphylaxis reactions: Treat as per ALS pathway with adrenaline, steroids and anti-histamines
Type 2 Complement Mediated Non-specific symptoms	<ul style="list-style-type: none"> Detection of antibodies on serum analysis where available 	<ol style="list-style-type: none"> Symptomatic treatment Consider stopping treatment
Type 3 Immune-Complex Mediated Serum sickness	<ul style="list-style-type: none"> Difficult to detect on assays, immune complexes known to adhere to membranes 	<ol style="list-style-type: none"> Symptomatic treatment Consider stopping the drug and switch if antibodies are confirmed
Type 4 T-Cell Mediated Delayed hypersensitivity reaction (after 24 hours up to 14 days post-infusion).	<ul style="list-style-type: none"> Clinical diagnosis 	<ol style="list-style-type: none"> Symptomatic management Consider stopping drug

Anti – TNF: Anti-Tumour Necrosis Factor; ALS: Advanced Life Support

Haematological effects

Leucopenia

Neutropenia has been reported in anti-TNF α treatment-exposed patients, with up to 20% of patients developing neutropenia on at least one occasion¹³. TNF α up-regulates other pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor, involved in the differentiation and maturation of haematopoietic progenitor cells¹⁴. TNF α blockade could mediate bone marrow failure by inhibiting stem cell differentiation¹⁵. However, the reduction in neutrophil count following TNF α inhibitor therapy is not seen for other cells from the same lineage (myeloid progenitor cell), specifically basophils, eosinophils and monocytes. The risk of neutropenia is significantly higher in patients with a low baseline neutrophil count or a previous history of neutropenia^{13,16}.

Thrombocytopenia

Isolated thrombocytopenia following the use of anti-TNF drugs^{17,18} has been reported. There are multiple hypotheses as to the possible aetiology, including autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes triggering the complement cascade, another unknown autoimmune mechanism, or idiosyncratic reaction¹⁸.

Anaemia

Anaemia is considered a marker of active disease in IBD and therefore clinicians need to first consider this as an aetiology. The incidence and prevalence of anaemia was approximately 19% and 28% respectively, in a recent population based cohort study. Crohn's with stricturing disease and long-standing UC were recognised as risk factors¹⁹. One study showed only marginal improvement in anaemia after treatment with anti-TNF therapy suggesting that disease activity in itself has a major role to play²⁰.

In this section, anaemia directly attributable to biologics is discussed, which is rare. There are sporadic case reports of aplastic anaemia with infliximab, more commonly in patients with rheumatoid arthritis than IBD²¹. A single case of infliximab induced autoimmune haemolytic anaemia (in a patient found to be anti-nuclear antibody (ANA) positive 1:40) has also been reported²².

Management of haematological effects

All patients starting anti-TNF therapy should have a baseline complete blood count with repeat testing every three to six months. At the onset of neutropenia, the anti-TNF should be withheld if the neutrophil count is deemed too low by the clinician. The patient should be left drug-free until neutrophil counts recover & anti-TNF therapy restarted when deemed clinically safe. Neutropenia can occur in patients managed with combination therapy with an anti-metabolite and this should be borne in mind and should be discontinued first. A neutrophil count less than 1000/mm³ should raise concern and <500/mm³ should lead to discontinuation of incriminating drugs and close monitoring. Rare anti-TNF induced systemic lupus erythematosus should be excluded and sargramostim is rarely necessary after drug discontinuation.

Thrombocytopenia can be managed by drug cessation, corticosteroid therapy or rescue therapy with intravenous immunoglobulin (IVIG). Thrombocytopenia has been reported to be prolonged after cessation of therapy. In severe cases this could persist for up to 6 months and also preclude exposure to any further anti-TNF agents¹⁸. This is likely to be a class effect and re-challenge with same class could be risky and therefore discouraged¹⁷. In severe cases, specialist haematology input is suggested.

Anaemia in IBD is more commonly seen due to ongoing disease activity. Clinicians should first consider assessment for disease and strategies to control and manage anaemia secondary to disease as per guidelines. As anaemia related only to therapy is rare, there is no specific guidance in current literature regarding future therapy with anti-TNF. Cessation of therapy would depend on

1 careful physician-patient discussion taking into account the severity of anaemia and alternative
2 treatment strategies. Involving haematologist in refractory cases would be prudent. (Table 2)
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Table 2- Haematological complications with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Leucopenia	<ul style="list-style-type: none"> Blood count monitoring 	1. If < safety threshold: stop drug, monitor blood count
Neutropenia		2. Restart drug when counts are within normal range
		3. Monitor
		4. Consider G-CSF
Thrombocytopenia	<ul style="list-style-type: none"> Blood count monitoring Establish temporal relationship to drug Secondary cases of low platelets to be excluded including concomitant drug therapy 	1. If < safety threshold: stop drug, monitor platelet count
		2. Consider IV immunoglobulins & steroids
		3. Consider switching to different class of biologic
Anaemia	<ul style="list-style-type: none"> Blood count monitoring Bone marrow aspiration in refractory cases 	1. If aplastic anemia: withdraw and stop drug
Drug related anaemia is rare but aplastic anaemia can be serious		2. Refractory cases warrant specialist hematology assessment

G-CSF- Granulocyte-Colony Stimulating Factor

Dermatological effects

In addition to skin malignancies anti-TNF therapy can cause a wide range of dermatological conditions. Most notably they include local skin irritation or reaction, increased skin infection rates, psoriasis, eczema, acne, and alopecia. Other rare dermatological complications include erythema nodosum²³, granuloma annulare and interstitial granulomatous dermatitis. Although some of the above complications are also seen as extra-intestinal manifestations of disease, temporal association with biologic therapy should help differentiate disease related complications from drug related complications.

Psoriasis and psoriasiform reactions can occur directly as a result of anti-TNF α therapy, which interestingly is used by dermatologists to treat severe cases of psoriasis. Psoriasis is a relatively common side effect of anti-TNF α therapy, with 1.5-5% of patients developing this manifestation²⁴. It is seen most commonly in females, typically 2-6 months following initiation of therapy²⁵. A nationwide cohort study reported incidence rates of anti-TNF induced psoriasis in IBD at 0.5% per patient-year²⁶. A more recent study shows a much higher incidence at 10.5%²⁷, but psoriasiform lesions are more common than psoriasis and have distinctive features. According to current evidence, females, smokers and patients with fistulising disease appear to be at risk²⁷. In addition to anti-TNF α induced psoriasis, psoriasiform and drug-induced psoriasiform lesions have been well recognised. Psoriasiform drug reactions can be distinguished histologically from psoriasis and resolve swiftly on cessation of drug therapy. Re-challenge results in recurrence of the lesions. The psoriasiform lesions could be secondary to infections and resolve on its treatment, though the infective origin of these are not always clear nor are their implications²⁵.

The exact mechanism triggering de novo psoriasis is unclear, although it has been postulated to be secondary to increased cutaneous expression of interferon alpha (IFN α). IFN α is released from dendritic cells to recruit T cells and pro-inflammatory cytokines IL-12 and IL-23. TNF α would

1 normally block IFN α expression and so anti-TNF α results in up regulation of IFN α ²⁴. Higher levels
2 of IFN are seen in anti-TNF α induced psoriasis than idiopathic psoriasis²⁵.
3
4

5 *Management*

6
7
8
9 Management of psoriasis due to anti-TNF α depends on severity of symptoms. Milder cases of
10 psoriasis can be treated clinically with topical therapy without cessation of anti-TNF, however more
11 severe cases may require anti-TNF α withdrawal²⁴. About 80% of patients respond to a combined
12 approach of steroids and biologics withdrawal²⁶. The use of another anti-TNF α agent may result in
13 recurrence of psoriasis in majority of cases (52%)²⁵. Ustekinumab has been used in the treatment
14 of CD²⁸ and psoriasis²⁹. There have been rare reports of paradoxical worsening of psoriasis with
15 ustekinumab but not known to cause drug-induced psoriasis²¹. Ustekinumab is potentially an
16 attractive option for treatment of refractory anti-TNF α induced psoriasis²⁵ requiring withdrawal of
17 primary drug. Methotrexate has been used but does not appear to be effective in all cases²⁶. It is a
18 useful option to have in selected cases. (Table 3)
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 3- Dermatological adverse effects with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Psoriasis Relatively Common (1.5% - 5% of patients on anti-TNFs)	<ul style="list-style-type: none">Clinical diagnosisHistology of skin lesionsEstablish temporal relationship between initiation of biologic therapy and development of psoriasis	<ol style="list-style-type: none">Specialist involvement from dermatologyIn mild cases: topical steroid therapyIn severe cases: stop drug and consider alternatives such as MethotrexateUstekinumab for managing both conditions is a viable alternative
Psoriasiform lesions Common	<ul style="list-style-type: none">Clinical DiagnosisConsider skin infections causing the rash	<ol style="list-style-type: none">Consider stopping drug in severe cases.Responds well to cessation of drug therapyTreat skin infection as appropriate
Erythema Nodosum Granuloma Annulare Interstitial Granulomatous Dermatitis Very rare	<ul style="list-style-type: none">Clinical Diagnosis	<ol style="list-style-type: none">No clear evidence on management as these conditions are rareSpecialist dermatology involvement is advisedUsually not necessary to withhold or stop drugClinician decision based on risk: benefit assessment

Anti – TNF : Anti-Tumour Necrosis Factor ;

Autoimmune-like disorders

Autoimmune-like disorders/syndromes are a group of conditions observed in patients on anti-TNF therapy. This was first described in initial studies of infliximab in patients with rheumatoid arthritis³⁰. These disorders include a variety of conditions such as positive antibodies e.g. –anti-nuclear antibodies, anti-double stranded DNA antibodies (dsDNA) (commonly IgM type), on immunological testing, various systemic or organ-specific autoimmune diseases as documented in the BIOGEAS registry, drug-induced systemic lupus erythematosus (DIL) called lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optical neuritis & inflammatory ocular disease, multiple sclerosis (MS)-like central nervous system (CNS) demyelination and peripheral neuropathies³¹.

William et al described anti-TNF α induced lupus (ATIL) based on the severity of symptoms displayed and suggested that ATIL is a distinct syndrome in itself³² and are likely to be different from drug induced lupus. In a pooled analysis across various diseases, studies which included patients with IBD showed that whilst ANA positivity was very common after anti-TNF therapy (40%-56%), asymptomatic anti-nuclear antibodies or anti-double stranded DNA antibodies require observation but not discontinuation of anti-TNF. The full range of symptoms of ATIL was seen in only about <1% of patients³². Most patients with full blown ATIL had fever, rash, arthritis and haematological abnormalities.

A large case series was reported by Costa et al comparing drug-induced lupus secondary to anti-TNF and classic drug-induced lupus³³. Both groups had similar systemic features and symptoms but there were some features that distinguished one group from the other. 72% of patients with anti-TNF drug-induced lupus had cutaneous manifestations compared to about 25% in classic drug-induced lupus group. Classic drug-induced lupus was not usually associated with antibodies to dsDNA and extractable nuclear antigen (ENA) or with complement consumption. 90% of anti-TNF α

1 drug-induced lupus patients were positive for anti-dsDNA antibodies and >50% had anti-extractable
2 nuclear antigen antibodies and decreased serum complement levels³³.
3
4
5
6
7
8
9

10 11 12 *Management*

13
14
15 The management of autoimmune-like disorders/syndromes secondary to anti-TNF therapy requires
16 a customised therapeutic approach according to severity of the induced autoimmune disease. ATIL
17 should be considered a distinct condition and managed accordingly. There are features which could
18 help distinguish this. The incidence/prevalence of dsDNA antibodies and hypocomplementaemia is
19 greater in ATIL, whilst anti-histone antibodies, the hallmark of classic drug-induced lupus, are less
20 commonly found³².
21
22
23
24
25
26
27
28
29

30 In patients with a positive ANA, it is not in itself an indication for discontinuation of therapy. In the
31 presence of mild features, cessation of therapy is probably sufficient. However, it can be continued
32 in patients with isolated cutaneous lesions or immunological alterations in whom biologics are
33 thought to be essential to treat underlying disease, with closer follow-up. In patients with involvement
34 of internal organs (kidney, lungs, nervous system), cessation of therapy is mandatory with addition
35 of corticosteroids and/or immunosuppressive agents^{30,33}. After discontinuation of the incriminating
36 anti-TNF the prognosis is generally very favourable. The presence of diagnosed SLE is a
37 contraindication to anti-TNF exposure.
38
39
40
41
42
43
44
45
46
47
48

49 Cardiac effects

50
51
52 It was reported that worsening cardiac failure was a possible adverse event in a randomised
53 controlled trial investigating the use of anti-TNF α therapy in cardiac failure³⁴. Majority of patients
54 enrolled were New York Heart Association III (NYHA) at baseline and the group receiving high dose
55
56
57
58
59
60

infliximab (10 mg/kg) were adversely affected with an increased likelihood of hospitalization, high frequency of worsening heart failure, with the risk of adverse clinical events persisting for up to five months after cessation of therapy³⁴. The exact mechanism of heart failure with anti-TNF α use remains unclear.

There have been case reports of second degree and complete heart block after infliximab therapy but are rare³⁵. This is more likely to happen in rheumatological conditions as there may be underlying cardiac involvement. A single blind prospective study which included rheumatological conditions concluded that new-onset cardiac arrhythmias, particularly ventricular tachyarrhythmia, developed during infliximab infusion, but their incidence did not achieve statistical significance³⁶. Acute coronary syndrome following infusion has been reported but this too is very rare³⁷. The rarer cardiac effects are based on reports with a very small number of patients, mostly from the rheumatology cohort who are at higher risk of having cardiac disorders.

Management

Current guidance recommends that use of anti-TNF therapy is best avoided in those with NYHA III/IV heart failure³⁸. All patients who develop heart failure while on an anti-TNF agent should discontinue therapy, conventional medication for treatment of heart failure started and specialty advice sought. An alternate class of agent should be considered for the primary disease process. It is still unclear whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYHA class I/II) ³⁸. For patients commencing anti-TNF therapy who have specific cardiac risk factors such as hypertension, valve disorders or ischemic heart disease, our recommendation is that clinicians should get a baseline electrocardiogram to record QT interval among other features and clinically assess the patient for any features of pre-existing heart failure that may preclude therapy. Not all studies have substantiated an association of anti-TNF therapy with heart failure and this is rare in patients with IBD.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Table 4- Cardiac adverse effects with anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Cardiac Failure More commonly seen in the treatment of rheumatological conditions; less so with IBD	<ul style="list-style-type: none"> Clinical diagnosis Objective assessments with investigations 	<ol style="list-style-type: none"> Avoid anti-TNFs in NYHA III and IV heart failure If drug precipitates heart failure: stop the drug Treat for heart failure with diuretics and early specialist involvement Switch to another class of drugs
Second and third-degree Heart Block More commonly seen in the treatment of rheumatological conditions; less so with IBD	<ul style="list-style-type: none"> 12 Lead ECG Cardiac monitoring 	<ol style="list-style-type: none"> Monitor patients for features of decompensation Specialist involvement for further management Stop drug and switch to another class
Arrhythmias More commonly seen in the treatment of rheumatological conditions; less so with IBD	<ul style="list-style-type: none"> 12 Lead ECG Cardiac monitoring 	<ol style="list-style-type: none"> Usually transient and does not need any specific management If transient episodes are self-limiting: consider continuing drug If persistent: seek specialist cardiology opinion

Anti – TNF : Anti-Tumour Necrosis Factor NYHA-New York Heart Association

1 **Neurological effects**

2
3
4 *Demyelination*

5
6
7 Demyelination has been recognised as a complication of anti-TNF therapy. A review of FDA
8
9 adverse event recording system showed that among 772 reports of neurological complications, 18%
10
11 of patients had IBD. About 36% of patients had received infliximab and peripheral neuropathy was
12
13 the most commonly reported event³⁹. Demyelination can occur in central or peripheral nervous
14
15 systems⁴⁰. It is unclear as to whether the relationship is truly causal, or whether anti-TNF triggers
16
17 an existing tendency for demyelination.
18
19

20
21
22 *Management*

23
24
25 The patients who have a family history of demyelination disorders may be at higher risk and this
26
27 should be considered before the therapeutic agent is chosen⁴¹. It is standard guidance to avoid anti-
28
29 TNF therapy in patients with concomitant multiple sclerosis or history of optic neuritis. In patients
30
31 who develop neurological deterioration and suspected demyelination during therapy, treatment with
32
33 biologic agent should be discontinued⁴¹ and specialist neurology opinion should be sought. The
34
35 clear relationship between demyelinating events and anti-TNF can be difficult to establish as IBD
36
37 may also be associated with demyelination. Treatment with corticosteroids, IVIG and
38
39 plasmapheresis are rarely necessary. (Table 5)
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 5- Neurological reactions with anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Demyelination Known to worsen demyelination in patients with multiple sclerosis	<ul style="list-style-type: none"> • Clinical diagnosis • Nerve Conduction Studies • MRI 	<ol style="list-style-type: none"> 1. Stop drug and consider alternatives 2. Seek specialist Neurology involvement 3. Consider pulse therapy with high dose methylprednisolone 4. Consider IV Immunoglobulin
MRI-Magnetic resonance imaging		

Infections and management strategies

Biologics are strong immunosuppressive agents and can increase risk of infection depending on their mechanism of action. TNF α is essential for activation, differentiation and recruitment of several immunological cell types; it has a role in granuloma formation, maintenance of granuloma integrity⁴² and host response to mycobacteria and intracellular organisms⁴³. A recent meta-analysis found that anti-TNF therapy was associated with a greater infection risk than placebo in treating UC but anti-integrin therapy was not; neither class showed an increased infection risk over placebo in CD⁴⁴. Other studies have confirmed increased risk in both forms of IBD.

A recent systematic review by Wheat et al concluded that at present there is no evidence of a higher odds of serious infection from the newly available biologic therapies such as vedolizumab and ustekinumab compared to anti-TNFs⁴⁵. Feagan et al report that infections in patients exposed to ustekinumab for CD is no higher than placebo in UNITI trials⁴⁶ and Wils et al reported 1 serious pulmonary infection in a cohort of 122 ustekinumab patients, followed up over 2 years⁴⁷. Bye et al reported an increased risk of Clostridium difficile infection with vedolizumab therapy but concomitant steroid and narcotic analgesics were identified as risk factors⁴⁸.

Bacterial infections

Patients receiving anti-TNF therapy have been reported to acquire both common and uncommon bacterial infections. Common sites for infection include upper and lower respiratory tracts, skin and subcutaneous tissue, urinary tract and GI tract⁴⁹.

Management

Common infections are treated with oral antibiotics as per local guidelines. A pragmatic approach would be to have a lower threshold to start treatment and switch to intravenous drugs in the presence of systemic symptoms. In severe sepsis requiring prolonged antimicrobial treatment, anti-TNF

therapy may have to be withheld. Restarting therapy can be considered once patients are afebrile, white cell counts within normal range and relevant imaging (CT, MRI pelvis) show no evidence of infective source. (Table 6)

Uncommon infections

Several non-mycobacterial intracellular infections, including listeriosis caused by *Listeria monocytogenes* and legionnaires' disease most often caused by *Legionella pneumophila*, have been associated with anti-TNF therapy⁵⁰. Listeria sepsis and meningitis has been described in patients receiving anti-TNF drugs⁵¹ and in 2011, the FDA added a boxed warning about the risk of listeriosis and legionnaires' disease for the entire class of TNF α inhibitors⁵². There are a few case reports of listeriosis complicating anti-TNF therapy. Listeriosis carries significant mortality, therefore requiring prompt diagnosis and aggressive treatment. The risk appears to be higher during the first year of therapy⁵³. Anti-TNF should be discontinued till the patient recovers from listeriosis.

Management

Suspicion of infection requires confirmatory testing and treatment using standard antibiotic regimes depending on pathogen isolated. Listeriosis is more likely to be seen in patients consuming mould-ripened cheese regardless of whether it is from pasteurised or unpasteurised milk and also from cold smoked gravad fish⁵⁴. In one study from USA, unpasteurised milk and dairy products were noted to significantly increase the risk of infections caused by *E-coli*, *Salmonella* and *Campylobacter*⁵⁵. In view of this overall increased risk of infections, it is safer for patients to avoid consumption of unpasteurised milk whilst on anti-TNF drugs.

Mycobacteria and tuberculosis

Tuberculosis (TB) caused by mycobacterium bacilli is a serious infection which carries significant morbidity. TNF α is necessary for a Th1-based cell-mediated immune response important in

activating macrophages to kill intracellular mycobacteria, and limit spread by formation of granulomas^{56,57}. The majority of exposed immunocompetent hosts have latent TB (LTB) which can subsequently lead to reactivation of infection if there is compromise to the immune system, such as initiation of anti-TNF drugs⁵⁸. It is therefore critical to identify and treat LTB prior to starting anti-TNF therapy⁵⁸.

An association between anti-TNF therapy and development of TB was noted when the FDA MedWatch spontaneous reporting system demonstrated 70 TB cases in a median of 12 weeks after initial infliximab exposure, in 2001⁵⁹⁻⁶⁸. Both extra-pulmonary and disseminated TB are more common in patients treated with anti-TNF therapy, compared with immunocompetent patients⁵⁹⁻⁶⁰. It has been hypothesised that the early occurrence of TB after infliximab may suggest reactivation of LTB rather than a de novo infection⁶⁰. Due to the high risk of reactivation, screening for TB is recommended prior to starting anti-TNF α .

The diagnosis of LTB can be difficult and should include a combination of detailed history and supportive investigations. At present, IGRA (interferon gamma release assay) and TST (tuberculin skin test) are commonly used in most centres. In a study by Mariette et al which looked at how effective the available tests are, it was noted that when one of the IGRA tests replaced TST, it influenced the decision made by physicians, leading to 28% fewer patients receiving anti-TB (ATB) prophylaxis⁶¹. This is likely because IGRA tests are more specific. As per this study, IGRA does not appear to be affected by corticosteroid or immunosuppressant therapy⁶¹. However, this may not always be the case as shown in an ex vivo study in which corticosteroids and infliximab reduced the performance of IGRA⁶². At present, IGRA is possibly more reliable than the other options available. TST is less specific and can be less frequently positive due to corticosteroid or immunosuppressant therapy and this should be borne in mind. Based on their findings, Mariette et al proposed the an algorithm for assessing patient, which is now generally applied prior to starting anti-TNF α therapy⁶¹. All patients should undergo appropriate history +/- chest x-ray. For those with a positive history or

x-ray, treat with ATB prophylaxis. For those with negative history, check with IGRA test (authors recommend GOLD, followed by T-SPOT if indeterminate). Those with negative results require no further screening. Those with positive results require ATB prophylaxis. Patients with indeterminate GOLD and T-SPOT test should undergo TST testing. Negative results require no further action, but a positive TST should be treated with prophylaxis⁶¹.

In patients who have a positive TST and negative IGRA, the degree of clinical suspicion should guide management, based on history and chest x-ray with a very low threshold to treat the patient. Generally, performing both TST and IGRA is not recommended. An initial indeterminate borderline IGRA can be followed up with TST and if the latter is positive the patient should be treated. The CDC recommend testing with either IGRA or TST, but a combination of both may be appropriate where clinical suspicion of LTB is high, or risk of subsequent LTB reactivation may result in a poorer outcome (such as those on immunosuppressants)⁶³.

Management

Guidelines by European Crohn's and Colitis organisation (ECCO)²⁶ and British Thoracic Society (BTS)⁵⁸ on screening and management of TB are similar in principle, suggesting treatment of LTB prior to initiation of anti-TNF therapy with a complete therapeutic regimen. If there is clinical suspicion +/- radiographic changes suggestive of TB, patients should be referred for treatment of LTB⁵⁸. Other patients should undergo LTB screening tests. The optimal screening strategy for these patients is still debatable.

After diagnosis of latent TB in a patient with IBD, appropriate treatment should be administered for at least 3 weeks prior to commencement of anti-TNF therapy^{64,65}; however if treatment with anti-TNF therapy is considered very urgent simultaneous treatment for latent TB and IBD may be considered. Alternative therapies such as vedolizumab or ustekinumab may also be considered for UC or CD. Short latent TB therapies are increasingly considered such as rifampicin for 4 months or isoniazid plus rifampicin for 3 months as adherence to 9 months of daily isoniazid poses

1 challenges^{66,67}. Exposure to active TB during anti-TNF therapy should lead to prompt re-evaluation
2
3 for latent or active TB. In case of active TB, anti-TNF should be discontinued and active TB treated.
4
5 If absolutely necessary, anti-TNF may be resumed after at least 2 months of anti-TB therapy with
6
7 satisfactory response, though it may sometimes be resumed earlier if absolutely necessary.
8
9 Increasingly other monoclonal antibodies such as ustekinumab or vedolizumab are being
10
11 considered. Annual re-testing for LTB in patients on anti-TNF therapy depends on risk factors for
12
13 exposure to TB and desirable in geographical areas with endemic TB. (Table 6)
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
<i>Common bacterial infections</i>		
Respiratory Tract	<ul style="list-style-type: none">• Clinical diagnosis• Relevant investigations depending on symptoms	1. Appropriate antibiotics based on site of infection
Urinary Tract		2. Consider early therapy
Gastrointestinal		3. If any signs of sepsis: stop drug
Cellulitis		4. Restart biologics when good evidence of resolved infection. (WCC, imaging)
<i>Serious Bacterial Infections:</i>		
Listeriosis	<ul style="list-style-type: none">• Serology• CT/MRI of brain• Lumbar puncture if meningitis suspected	1. Appropriate antibiotics based on sensitivity
Legionnaires' disease		2. Seek specialist microbiology advice
Septic Arthritis		
Septicemia		
<i>Tuberculosis (TB):</i>		
Latent TB Re-Activation	<ul style="list-style-type: none">• Risk assessment based on initial screening with Quantiferon or T-Spot Testing• Thorough history and risk factor assessment• Chest X-Ray	<ol style="list-style-type: none">1. If positive or indeterminate: involve specialists2. Treat as per ECCO guidelines and British Thoracic Society Guidelines3. Risk: Benefit analysis by clinician4. Consider alternative therapy i.e. vedolizumab or ustekinumab

WCC-white cell count

Viral infections

A majority of human viral infections are self-limiting but some are capable of causing chronic infection [e.g. human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)]. There are viruses linked to malignancy, such as Epstein-Barr virus (EBV) and human papilloma virus (HPV). EBV will be discussed in more detail in 'malignancy' section of this text.

Varicella (VZV) and Shingles

This can present with severe or disseminated disease if contracted while on anti-TNF therapy⁶⁸. In one study, the prevalence of prior varicella zoster virus (VZV) infection among IBD patients was greater than 90%⁶⁹ and it was not noted that a significant number had a VZV IgG negative status. It is known that patients with IBD are at a higher risk of VZV infection and more so when on immunosuppressive therapy^{70,71}.

Herpes zoster or shingles is caused by reactivation of VZV. The incidence of shingles is again increased in patients with IBD, the elderly population at particular risk. In a study looking at herpes zoster in IBD, it was seen that patients with CD were at higher risk; age >45 years, treatment with corticosteroids for >2 weeks, thiopurine therapy were associated with increased risk of infection⁷². Long et al reported similar findings and also noted that patients on anti-TNF therapy for IBD are at higher risk of herpes zoster with an odds ratio of 1.81 (95% CI: 1.48-2.21)⁷³.

Management

Immunocompromised patients exposed to VZV should be treated with VZV immunoglobulin⁷⁴. Patients who contract VZV or shingles during a period of immunosuppression require antiviral therapy. If oral therapy is appropriate, valganciclovir should be considered as this provides higher oral bioavailability than aciclovir⁷⁵. (Table 7)

Prevention of infection is possible due to availability of effective vaccines. It is recommended that all patients are screened for evidence of past infection prior to starting biologics or immunosuppressives including steroids. ECCO suggest that in seronegative patients two-dose course of varicella vaccine should be given at least 3 weeks prior to commencement of therapy⁶⁵. If subsequent immunisation is necessary, it can be administered after a 3–6 month cessation of all immunosuppressives as both the VZV and shingles vaccines are live vaccines⁷⁵, although there is emerging evidence that administration of live zoster vaccine to patients already on anti-TNF therapy did not result in disease and there was expected immune response to the vaccine⁷³.

Hepatitis B

TNF α and interferon (IFN) γ are released by cytotoxic T lymphocytes on antigen recognition of the hepatitis B virus, activating two viricidal pathways, plus antigen non-specific T cells & macrophages⁷⁶. Reactivation of HBV may occur during anti-TNF therapy, or on subsequent withdrawal (secondary to immune reconstitution). Reactivation of chronic HBV carriers (hepatitis B surface antigen (HBsAg) positive, undetectable HBV DNA, normal LFTs) after anti-TNF therapy has been reported⁷⁷. Patients who have had HBsAg seroconversion following exposure to HBV [HBsAg negative, anti-HBc (core antibody) positive and anti-HBsAg antibody positive] have been successfully treated with anti-TNF therapy without HBV reactivation during follow up⁷⁸. Chronic active HBV patients already successfully controlled with antiviral therapy prior to introduction of anti-TNF show no deterioration in the viral load or liver enzymes^{79,80}. A comprehensive review by Pattullo⁸¹ looked at incidence & prevalence of HBV reactivation in IBD when treated with immunosuppressants without HBV prophylaxis; risk stratification of patients was also done based on type of biologic therapy⁸¹. The incidence of immunosuppression related HBV reactivation was noted to be about 36% in HBsAg positive patients. The overall prevalence of HBV in IBD ranged from 0.6-17% for HBsAg positive patients, and 1.6-42% for HBsAg negative/anti-HBc positive

patients. The risk estimate of HBV reactivation was reported to be moderate (1-10%) with anti-TNF⁸¹.

Management

All patients should be screened prior to initiation of therapy, although which patients should receive antiviral therapy remains unclear. Screening should be carried out checking for hepatitis B surface antigen, antibody to surface antigen & anti HB core antibody levels and if HBsAg or anti-HBc is positive, DNA quantification should be done⁶⁵. Chronic HBV carriers and those with HbsAg seroconversion should be considered for antiviral therapy and hepatology involvement. It is recommended that patients who are due to start biologics (moderate risk) are given anti-viral prophylaxis if they are HBsAg positive and continued for at least 6 months after completion of immunosuppressive therapy⁸¹. In case of reactivation, it is recommended that one of the antivirals is started and continued for at least 6 to 12 months after immunosuppressive therapy has been stopped. The antiviral medication of choice may depend on the patient's individual circumstances, and the planned duration of immunosuppression⁸². Entecavir and tenofovir are now preferred antivirals in IBD patients due to their rapid onset of action, highest anti-viral potency with low incidence of resistance⁶⁵. Whilst lamivudine is used, this has its limitations if long term therapy is required, as resistance can occur in up to 30% of patients after 1 year and 70% after 5 years⁸². Peginterferon-alpha-2a (IFN α) is best avoided due to the risk of myelosuppression and also risk of exacerbating CD⁶⁵.

Hepatitis C

TNF α appears to be involved in the pathogenesis of HCV, with patients with higher serum TNF α levels less likely to respond to anti-viral therapy⁸³. TNF α blockade may increase reactivity of peripheral T cells to antigen stimulation⁸³. Biologics have an acceptable safety profile for use in

patients with HCV and is not contraindicated in concomitant HCV infection. However, in the presence of acute HCV, anti-TNF therapy is contraindicated⁸⁴. In the presence of chronic HCV, the decision to treat with anti-TNF depends on liver synthetic function. It is best avoided in patients who are Child-Pugh category B or C⁸⁴. HCV patients being treated with anti-TNF therapy should have close monitoring of aminotransferases with consideration for discontinuation of treatment with continued elevations⁸³. The guidelines from ECCO suggest cautious use of antivirals due to drug interactions⁶⁵. Infection diagnosed whilst on anti-TNF therapy does not necessarily require cessation of therapy⁶⁵. There is no data yet on the use of newer antivirals for HCV in the context of biologics use for IBD but there are no contraindications for their concurrent use.

Management

The ECCO guidelines are equivocal about screening for HCV prior to use of immunosuppressive therapy⁶⁵. However, it would be prudent to screen patients who are likely to need biologics considering the high curative rates with newer anti-viral drugs for HCV. All patients with HCV infection should be discussed and managed jointly with hepatology services, especially when biologics are indicated for IBD. During the course of therapy, close monitoring of liver functions is key.

HIV infection

The interaction between TNF α and the human immunodeficiency virus (HIV) has been the subject of much scrutiny. The molecular pathway by which HIV expression is upregulated by TNF α is well described^{85,86}. Despite these findings, use of anti-TNF in HIV-patients must be balanced with a potential increase in the risk of opportunistic infections in patients with an attenuated immune system.

The evidence base for advice regarding use of biologics in patients with HIV and IBD is limited. Within a cohort study and several case reports, biologic therapy with infliximab in refractory IBD

patients has been demonstrated to be effective in inducing disease remission with only a minority experiencing adverse effects⁸⁷⁻⁷⁷. It is important to note that initial CD4+ count in patients included in these studies are > 200 cells/mL. The ECCO guidelines⁶⁵ also suggest that the HIV-IBD cohort of patients are less predisposed to infection on highly active anti-retroviral therapy (HAART) than if they did not receive HAART. In this cohort, adverse effects have presented as either a pre-disposition to infections, deranged CD4+ count or HIV viral loads.

Abreu et al describe an HIV positive, thiopurine-intolerant patient treated with IFX for a UC-flare unresponsive to steroids⁸⁸ who had been on ART (emtricitabine/tenofovir/efavirenz) with undetectable HIV viral load & CD4+ count of 357/mm³ prior to infliximab therapy. Although excellent disease response was achieved, he was diagnosed with listeriosis and was successfully treated. (CD4+ count 350/mm³). Infliximab was restarted with no clinical consequences. It is likely these patients with IBD remain at increased risk of opportunistic infections⁸⁹.

Other examples of adverse effects of biologics in HIV are reported in the rheumatology cohort⁹⁰. In one case series⁹¹, a patient who was not on HAART therapy was observed to have an increase in viral load (22,148 c/ml to 428,503 c/ml) following initiation of infliximab therapy. This required temporary cessation of infliximab and the rise was not observed at re-administration.

Within the limited evidence available, it is noted that patients do benefit from adequate disease response with no specific HIV-related complications. Due to risk of AEs, it is recommended that screening for HIV is undertaken prior to treatment with biologics and patients with IBD recognised as HIV positive are managed by a multi-specialty team. Generally, in the absence of other infections treatment of HIV infected patients with anti-TNF is relatively safe. This group of patients must ideally be on HAART. A discussion about potential increased risk of infection, baseline blood tests including CD4+ count (ideally 200 cells/mL+), and HIV viral load is necessary. Close monitoring throughout duration of therapy is key. An Increase in HIV viral load needs discussion with specialists and discontinuation of biologic may become necessary. Any overt sign of infection merits hospital

admission to identify and treat the infection source and biologics paused. Restarting biologics should be discussed based on clinical aspects of each case. (Table 7)

For Peer Review

Table 7- Viral infections in the use of anti-TNF therapy

Complication	Diagnosis	Management Strategy
Varicella Relatively common	<ul style="list-style-type: none">Clinical diagnosisSerology testing available	<ol style="list-style-type: none">Treat with varicella immunoglobulinAntimicrobial therapy with valganciclovir
Chronic Stable HBV Reactivation of chronic infection	<ul style="list-style-type: none">Screening for HBV mandatoryClose monitoring of liver function and viral load	<ol style="list-style-type: none">Joint care with HepatologistMay require treatment with antiviralsBiologics can be continued unless acute fulminant liver failure suspected
Chronic Active HBV on antiviral therapy	<ul style="list-style-type: none">Screening for HBV mandatoryClose monitoring of liver function and viral load	<ol style="list-style-type: none">Continue antiviralsEntecavir and tenofovir drugs of choice
Hepatitis C	<ul style="list-style-type: none">Screening for HCV recommended prior to anti-TNF therapyClose monitoring of LFTs and HCV RNA Load in HCV infected patients	<ol style="list-style-type: none">Joint care with HepatologistContinue biologic with close monitoringNo contraindication for therapy
Cytomegalovirus (CMV)	<ul style="list-style-type: none">Check serology for CMV IgM and viral PCRSupported by tissue diagnosis with histology and immunohistochemistry	<ol style="list-style-type: none">Treatment with IV ganciclovir and switch to oral valganciclovir for total of 2-3 weeksUse foscarnet as per sensitivitiesIf systemic CMV infection: consider stopping anti-TNF
Human Immunodeficiency Virus	<ul style="list-style-type: none">Close monitoring in addition to CD4+ counts	<ol style="list-style-type: none">Continue biologics when HAART established and CD4+ counts are above 350Consider withholding biologic when CD4+ <200Joint care with multidisciplinary decision approach

Anti – TNF : Anti-Tumour Necrosis Factor ; HBV-Hepatitis B virus; HCV-Hepatitis C virus; LFTs- liver function tests; PCR- polymerase chain reaction; HAART- highly active antiretroviral therapy

For Peer Review

Fungal infections

Patients with IBD are known to be at an increased risk of fungal infections. This is due to multiple factors such as severity of disease activity, comorbidities, treatment with opioids, surgery, poor nutritional status, leucopenia and older age⁹². Another factor is immunosuppressive therapy, important of which are anti-TNFs. A risk factor analysis by one recent systematic review reported anti-TNF therapy as the predominant factor associated with fungal infections⁹².

Aspergillosis

Aspergillosis, caused by *Aspergillus fumigatus* is a serious pulmonary infection which warrants prompt diagnosis and treatment. Attenuation of the inflammatory pathway through TNF α blockade alters the cytotoxic immune response to fungal infections and in aspergillosis, it is involved in polymorphonuclear leucocyte activation in response to infection⁹³. The evidence is mostly from case reports. In 2001, a case of invasive pulmonary aspergillosis was reported in a patient with CD on anti-TNF therapy⁹⁴. There have been other case reports since but overall, it appears to be a rare occurrence. This usually presents initially with a poorly productive cough and can progress to respiratory insufficiency; radiological changes are seen⁹⁴⁻⁹⁵.

Management

The definitive diagnosis is on culture of broncho-alveolar fluid. The infection is treated with prolonged anti-fungal therapy based on sensitivities; amphotericin B or voriconazole or caspofungin is used. The condition carries very poor prognosis. Concomitant tuberculous cavity needs exclusion. (Table 8)

Histoplasmosis

This is another potential opportunistic infection reported in patients exposed to anti-TNF treatment. In a case series of ten immunocompromised subjects from an area endemic with histoplasmosis, 9

contracted histoplasmosis shortly after commencing infliximab infusions. Clinical presentation can be varied and include pulmonary, extra-pulmonary or disseminated disease symptoms which are non-specific⁹⁶.

Table 8- Fungal infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Candidiasis Commonly localised infections but systemic and invasive infection can be life threatening	<ul style="list-style-type: none"> Serology, culture and molecular studies 	1. Localised infections: Topical therapy 2. Invasive infections: <ol style="list-style-type: none"> Stop biologic IV Fluconazole Seek specialist advice
Aspergillosis Pulmonary symptoms and invasive infection	<ul style="list-style-type: none"> Serology, culture and imaging 	1. Stop biologics 2. IV Anti-fungal therapy (Consider IV voriconazole) 3. Caspofungin is another option 4. Specialist involvement
Histoplasmosis Usually pulmonary infection	<ul style="list-style-type: none"> Serology, culture and radiology 	1. Stop biologic therapy 2. Treatment with either one of: <ol style="list-style-type: none"> Amphotericin B initially and step-down therapy to an azole preparation Itraconazole
Pneumocystis Jirovecii	<ul style="list-style-type: none"> Clinical diagnosis Culture, microscopic and molecular diagnosis 	1. Co-trimoxazole 960mg BD, if severe infection increases to 1.44 g BD 2. Specialist involvement

Management

Invasive fungal infections should be treated with systemic antifungals and all immunosuppressant medication should be reviewed. The FDA in 2008 have issued post market drug safety information alerting healthcare providers that invasive fungal infections and histoplasmosis in patients receiving anti-TNF drugs are not being swiftly recognised, resulting in possible delays to patient therapy. The FDA recommends the involvement of infectious diseases specialists⁹⁷ in the management of such cases. (Table 8)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Other Opportunistic infections

Cytomegalovirus (CMV)

CMV infection (detected by serology) could be due to reactivation of latent infection during immunomodulator or biologic therapy, but usually is itself mild or asymptomatic even on immunosuppressants. However, CMV colitis, retinitis, pneumonia or severe CMV infection during treatment of IBD requires further assessment⁷⁵ to plan management. Nevertheless, not all cases of CMV infection in anti-TNF use progress to CMV disease⁹⁸.

The diagnosis of CMV disease using histopathology with immunohistochemistry is highly sensitive and specific. This combined with CMV viral load (CMV DNA detected by PCR in serum & tissues) can provide most information about disease state⁷⁵. CMV viral loads of >250 copies/mg is a predictor for patients presenting with corticosteroid-resistant disease⁷⁵.

CMV disease manifesting as colitis is a recognised complication of IBD and should be screened for in those patients presenting with acute severe colitis⁹⁹. Typically, patients may have had previous exposure to immunosuppressive therapy and experienced prolonged corticosteroid therapy or corticosteroid-refractory disease. CMV can also be a cause of chronic pouchitis¹⁰⁰.

Management

It is important that diagnosis is established swiftly. When considered as a differential diagnosis, testing for CMV viral load with PCR is recommended to look for CMV disease especially in ill patients with systemic manifestations. Histology and immunohistochemistry may be used to support the diagnosis of CMV colitis. Once diagnosed, ECCO recommend a 2-3 week course of ganciclovir therapy for CMV disease, and immunosuppressants are withheld⁷⁵. However, a retrospective cohort case study of CMV-positive colitides, identified that patients with milder colitis were less likely to be treated, and could respond to standard immunosuppressive therapy without additional treatment for

CMV. CMV may be transiently reactivated and disappear without antiviral therapy. In one study it was noted that those with more severe disease were more likely to be treated with ganciclovir, and were more likely to require either rescue therapy or surgery, despite adequate treatment of CMV¹⁰¹. CMV colitis complicating UC leading to acute severe colitis can be challenging to manage. A study by Kopylov et al reported that the outcomes for patients with severe colitis. Patients received infliximab/ciclosporin with ganciclovir vs ganciclovir alone, and they had similar colectomy rates¹⁰². In patients who test positive for CMV whilst on anti-TNF therapy, there is a evidence that anti-TNF can be continued¹⁰³. (Table 7)

Pneumocystis pneumonia (PCP) or pneumocystis jirovecii pneumonia (PJP)

This is a serious infection reported in patients after use of immunosuppressants. A large population based cohort study looked at risk of PJP in IBD patients¹⁰⁴. Although there is some evidence that the overall hazard risk of PJP in IBD is higher than normal population, the absolute risk of PJP is considered to be very low (0.03% in their cohort)¹⁰⁴. In a large case series of PJP after infliximab use, mean onset of symptoms reported was 21 days although majority of patients were exposed to concomitant immunosuppressive therapy. Over a quarter (27%) of patients died¹⁰⁵ in these reported series, so early recognition and therapy is paramount. ECCO guidance recommends that patients on triple immunotherapy with one being a calcineurin inhibitor or anti-TNF should receive standard prophylaxis with Trimethoprim-sulfamethoxazole (co-trimoxazole) if tolerated. It should be considered in those on dual immunosuppression especially if one is a calcineurin inhibitor⁷⁵ and in anti-TNF regimens with associated corticosteroid use⁷⁵. However, pill-burden and side effects are to be kept in mind. Co-trimoxazole is an effective option for prophylaxis and active infection. Clinicians should discuss with their local microbiology and infectious disease departments. Although more recent studies report very low risk, clinicians have to be vigilant throughout the course of treatment and decision on prophylaxis has to be on a case-by-case basis. (Table 8)

Infection prevention and vaccination recommendations

The main focus of the article is on management of adverse effects and our stress on prevention though very important, is limited as these have been extensively addressed in ECCO guidelines. ECCO guidance recommends that prior to immunosuppression a detailed history and examination including prior bacterial, viral and fungal infections, particularly herpes, VZV, TB exposure, prolonged travel/stay or plans to travel to TB endemic or tropical areas and completion of childhood vaccination programmes. Further advice should include cervical smear screening for women, food hygiene and avoidance of raw and unpasteurised foods. Education on safe use and preparation of dairy & meat products can benefit patients at risk of *Listeria* infection whilst on anti-TNF α therapy. Live attenuated vaccines must be avoided on immunomodulator or anti-TNF therapy and ideally patients should receive annual inactivated influenza vaccine and pneumococcal vaccine as required. Prior to the onset of immunosuppression, consider vaccination with any outstanding routine vaccines plus HBV, VZV (if seronegative and no clinical history) and HPV⁷⁵. If patients require live vaccines during therapy, the risk: benefit assessment of vaccination should be undertaken. Patients are usually immunocompetent within 3-12 months¹⁰⁶ after cessation of therapy. Corticosteroid therapy alone is not considered to cause significant immunocompromise unless high doses (20mg or higher) have been used continuously for more than two weeks¹⁰⁶.

Malignancy

Malignancies thought to be linked to immunosuppressive agents and anti-TNF use include solid organ malignancies, non-melanoma skin cancer (NMSC), melanoma, lymphoproliferative malignancies, and those with viral association such as EBV-related lymphomas and HPV-related cervical cancers or dysplasia. However, difficulty remains in establishing a cause-effect relationship.

A possible association between anti-TNF use and malignancy first arose from post-marketing reports to the FDA. There were 26 cases of lymphoma reported in patients with rheumatoid arthritis or CD disease treated with etanercept or infliximab¹⁰⁷. Further studies demonstrated an increased risk for solid organ and NMSC in patients treated with anti-TNF and further immunosuppressive therapies¹⁰⁸. Many IBD patients are either on multidrug regimes or have had past exposure to thiopurines (or other immunosuppressants) prior to anti-TNF usage.

Historically most trial data is from the rheumatology population. A meta-analysis derived from nine clinical trials of patients receiving anti-TNF treatment or placebo identified a number needed to harm of 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months¹⁰⁹. The malignancy rates were significantly more common in those treated with higher doses ($\geq 6\text{mg/kg}$ of infliximab every 8 weeks or 40mg of adalimumab alternate weeks)¹⁰⁹. A more recent meta-analysis of 74 randomised controlled trials concerning adalimumab and infliximab showed no overall relative risk (RR) increase on short term follow up for malignancy with the exception of NMSC which had a RR of 2.02 (95% CI 1.11-3.95)¹¹⁰. A 6-year follow up study from the national Danish registers only identified three solid organ malignancies and one case of melanoma, with total follow up ranging from 0.1-72.1 months¹¹¹. The Crohn's therapy, resource, evaluation and assessment tool (TREAT) registry is collecting prospective data on large number of CD patients to evaluate the long-term safety of CD therapies. Data published from the registry in 2006 showed mortality rates to be similar

between infliximab and non-infliximab patient groups after a short period of follow up (mean follow up 1.9 years)¹¹². Subsequent data from the registry published in 2014 (with follow up of up to 7.6 years) has shown that none of immunosuppressants, infliximab or combination therapy to be an independent risk factor for malignancy¹¹³. However, the follow-up period remains short and future analysis of the registry is likely to provide further evidence.

The CESAME Study Group¹¹⁴ assessed the impact of thiopurine use on development of NMSC— comprised of basal cell carcinoma, squamous cell carcinoma and lymphoproliferative disorders (increased risk found in the thiopurine group). Although a large number of patients were included, the risk of malignancy secondary to biologics could not be assessed due to relatively small number of patients on these drugs¹¹⁵. A study by Long et al published in 2010 assessed risk of malignancy and concluded that IBD in itself increased risk of NMSC (incidence rate ratio IRR 1.64 95% CI 1.51-1.78) and a nested case-control model showed an increased risk because of recent biologic use among patients with CD (adjusted OR 2.07, 95% CI 1.28–3.33)¹¹⁶; patients on combination therapy had the highest OR compared to medication-free patients (OR 5.85 95%CI 3.2-10.8)¹¹⁶. Another study in 2012 reported that patients were at higher risk of melanoma when exposed to biologics and NMSCs were mainly related to thiopurine therapy¹¹⁷. The most recent French national cohort study showed an increased risk of lymphoma in treatment exposed patients. When compared with unexposed patients, the risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR, 2.60; 95% CI, 1.96-3.44; P < 0.001), anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60-3.64; P < 0.001), or combination therapy (aHR, 6.11; 95% CI, 3.46-10.8; P < 0.001)¹¹⁸.

There remains concern about cases of hepatosplenic T-cell lymphoma (HSTCL) (a rare and aggressive form of non-Hodgkin's lymphoma affecting predominantly young men) occurring following infliximab, adalimumab or thiopurine use. In a study published by Thai et al, they reported 22 cases of HSTCL in IBD and most were associated with thiopurine therapy either as monotherapy or in combination with anti-TNF. Whilst a link is recognised, quantifying this risk to individual patients

on current evidence is difficult¹¹⁹. They also concluded that despite the risk, benefits of treatment far outweighed the risks¹²⁰.

Secondly, observational studies have noted a potential predisposition to development of EBV related lymphoproliferative disorders in IBD patients, in particular those treated with thiopurines and anti-TNF α agents⁷⁵. Patients with EBV are predisposed to post-transplant lymphoproliferative disorders (PTLD), where T-cell immune surveillance is impaired⁷⁵. EBV related lymphomas may present in the gut, rather than nodal sites. Screening for EBV should ideally be considered, however there is no current vaccination for EBV naïve patients. In those developing EBV on therapy, treatment with antiviral medication and withdrawal of therapy should be considered⁷⁵. IBD itself does not appear to increase risk of lymphoma diagnosis¹²¹. However use of a thiopurine for IBD or combination therapy with an anti-TNF α may increase risk¹²¹. Establishing any isolated effect of anti-TNF α on lymphoma development is challenging. In a meta-analysis looking at lymphoma rates in CD patients treated with anti-TNF α , two thirds of all patients were also receiving immunomodulator therapies¹²²; anti-TNF α treated patients appeared to have an increased risk of lymphoma (SIR 3.23 95% CI 1.5-6.9) compared to the expected population rate¹²². The SIR was also increased when compared to previously studied patients on immunomodulator therapy alone (1.7 95% CI 0.5-7.1), however this did not reach statistical significance¹²². There were too few patients treated with isolated anti-TNF therapy to determine the individual risk of anti-TNF usage on lymphoma development¹²².

Management principles in malignancy

The association between various malignancies and anti-TNF treatment remains unclear, but it is important that patients' history of previous or pre-existing cancer is carefully documented prior to initiation of biologic treatment. The use of biologics as monotherapy can be considered in patients with previous history of cancer. Axelrad et al noted that at 5 years after prior cancer diagnosis no significant difference in cancer free survival could be demonstrated between IBD treatment with anti-

TNF monotherapy, immunosuppressant monotherapy, anti-TNF combined with thiopurine therapy, though numerically anti-TNF monotherapy had the least cancer recurrence¹²³. In a meta-analysis of 16 studies of immune mediated diseases, including 8 studies involving IBD patients, similar rates of cancer recurrence were observed among individuals affected by previous cancer who received no immunosuppressives, anti-TNF monotherapy, immunosuppressant therapy or combination therapies¹²⁴. Therefore, in patients with a history of cancer, recent or past, effective therapy for IBD can be used after consideration of risks & benefits and discussion with oncologists. ECCO guidelines also provide advice on managing IBD patients with previous history of malignancy¹²⁵. Generally, among biologics, monotherapy anti-TNF α , vedolizumab or ustekinumab may all be used, but often thiopurines are avoided.

Table 9- Malignancies with anti-TNF therapy

<u>Complication</u>	<u>Causative drug/s</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Melanoma	Anti-TNF	<ul style="list-style-type: none"> Clinical diagnosis Skin biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Non-melanoma skin cancer	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Clinical diagnosis Skin biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Lymphoma <ul style="list-style-type: none"> HSTCL PTLD 	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Cross sectional imaging Tissue Biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider switching drug class
Other malignancies: Leukoencephalopathy	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Clinical diagnosis Imaging Tissue Biopsy 	<ol style="list-style-type: none"> 1. Stop the drug 2. Consider switching drug class 3. Relevant Specialist involvement

Anti – TNF : Anti-Tumour Necrosis Factor ; HSTCL: Hepatosplenic T-cell Lymphoma; PTLD: Post-transplant lymphoproliferative disorder

CONCLUSION

The use of biologics is now standard therapy for IBD used either as monotherapy or in combination with immunomodulators. A review of safety data of currently used biologics show cumulative evidence for anti-TNF α as they have been used for longer duration. In summary, acute infusion reactions are common with anti-TNF, neutropenia is a worrying AE and may require temporary cessation of therapy. Infections are significantly higher with anti-TNF which include common and uncommon bacterial infections, mycobacterial infections (in particular TB), viral and fungal infections and opportunistic pathogens. Diagnostic and management strategies are outlined in separate tables.

Anti-TNF therapy causes a wide range of dermatological presentations. It is important to differentiate drug induced psoriasis from psoriasiform rash. Treatment may range from topical therapy to anti-TNF α withdrawal. Ustekinumab may be useful in these cases.

Malignancies thought to be linked to anti-TNF use include solid organ malignancies, NMSC, melanoma, lymphoproliferative malignancies, and those with a viral association. However, difficulty remains in attributing a causal relationship particularly given the confounding of thiopurine use. The link between HSTCL is recognised but currently not quantified due to scarcity of data. IBD increases risk for NMSC, with the risk further increased for in combination therapy. The risk of lymphoma is increased with combination therapy with thiopurines including EBV related lymphoma but it is to be noted that results from the TREAT registry suggest that none of the immunosuppressants, infliximab or combination therapy are an independent risk factor for malignancy. However, the follow up duration remains short. Biologics can be used in patients with prior history of cancer after careful discussion about risks and benefits with oncologists.

1 Finally, although these therapies are often very effective, they present unique challenges. It is likely
2 that in the future biologics will be used in a wider cohort of patients earlier in their disease journey,
3 and therefore prompt recognition of adverse events secondary to drugs is important. Further
4 reporting of rarer AEs and prompt recording of common AEs in registries will help assess risk more
5 accurately. This information should help clinicians inform their patients of risks associated with each
6 therapy and will lead to more informed decision making, thus improving patient care.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

REFERENCES

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance therapy for Ulcerative Colitis. *N Engl J Med*. 2005;353:2462-2476.
2. Wee JS, Petrof G, Jackson K, Barker JNWN, Smith CH. Infliximab for the treatment of psoriasis in the U.K.: 9 years' experience of infusion reactions at a single centre. *Br J Dermatol*. 2012;167(2):411-416. doi:10.1111/j.1365-2133.2012.10931.x.
3. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol*. 2003;98(6):1315-1324. doi:10.1111/j.1572-0241.2003.07457.x.
4. Ricart E, Panaccione R, Loftus E V, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol*. 2001;96(3):722-729. doi:10.1111/j.1572-0241.2001.03612.x.
5. Steenholdt C, Svenson M, Bendtzen K, Thomsen OØ, Brynskov J, Ainsworth MA. Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease. *J Crohns Colitis*. 2012;6(1):108-111. doi:10.1016/j.crohns.2011.08.001.
6. Matsui T, Umetsu R, Kato Y, et al. Age-related trends in injection site reaction incidence induced by the tumor necrosis factor- α (TNF- α) inhibitors etanercept and adalimumab: The Food and Drug Administration adverse event reporting system, 2004–2015. *Int J Med Sci*. 2017. doi:10.7150/ijms.17025.
7. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):96-109.e1. doi:10.1053/j.gastro.2013.06.010.
8. Duburque C, Lelong J, Iacob R, et al. Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. *Aliment Pharmacol Ther*.

- 2006;24(5):851-858. doi:10.1111/j.1365-2036.2006.03026.x.
9. Colombel J-F, Loftus E V., Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo Clinic experience in 500 patients. *Gastroenterology*. 2004;126(1):19-31. doi:10.1053/j.gastro.2003.10.047.
10. Nash P, Vanhoof J, Hall S, et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis. *Rheumatol Ther*. 2016. doi:10.1007/s40744-016-0041-3.
11. Truhlář A, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;95:148-201. doi:10.1016/j.resuscitation.2015.07.017.
12. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-Related Infusion Reactions: Systematic Review. *J Crohns Colitis*. 2015. doi:10.1093/ecco-jcc/jjv096.
13. Hastings R, Ding T, Butt S, et al. Neutropenia in patients receiving anti-tumor necrosis factor therapy. *Arthritis Care Res (Hoboken)*. 2010;62(6):764-769. doi:10.1002/acr.20037.
14. Beutler BA. The role of tumor necrosis factor in health and disease. *J Rheumatol Suppl*. 1999;57:16-21.
15. Keystone EC. Tumor necrosis factor-alpha blockade in the treatment of rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001;27(2):427-443.
16. Sebastian S, Ashton K, Houston Y, Diggory TM, Dore P. Anti-TNF therapy induced immune neutropenia in Crohns disease- report of 2 cases and review of literature. *J Crohns Colitis*. 2012;6(6):713-716. doi:10.1016/j.crohns.2012.01.014.
17. Salar A, Bessa X, Muñiz E, Monfort D, Besses C, Andreu M. Infliximab and adalimumab-induced thrombocytopenia in a woman with colonic Crohn's disease [7]. *Gut*. 2007;56(8):1169-1170. doi:10.1136/gut.2007.123547.

18. Casanova MJ, Chaparro M, Martínez S, Vicuña I, Gisbert JP. Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease. *J Crohns Colitis*. 2012;6(10):1034-1037. doi:10.1016/j.crohns.2012.04.001.
19. Eriksson C, Henriksson I, Brus O, et al. Incidence, prevalence and clinical outcome of anaemia in inflammatory bowel disease: a population-based cohort study. *Aliment Pharmacol Ther*. 2018. doi:10.1111/apt.14920.
20. Ioannis E. Koutroubakis, MD, Claudia Ramos–Rivers, MD, Miguel Regueiro, MD, Efstratios Koutroumpakis, MD, Benjamin Click, MD, Marc Schwartz, MD, Jason Swoger, MD, Leonard Baidoo, MD, Jana G. Hashash, MD, Arthur Barrie, MD, Michael A. Dunn, MD, and David G M. The influence of anti-TNF agents on hemoglobin levels of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(7):1587-1593.
21. Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Van Assche G. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther*. 2012;36(4):312-323. doi:10.1111/j.1365-2036.2012.05189.x.
22. Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor α treatment in Crohn's disease: a prospective cohort study. *Gastroenterology*. 2003;125(1):32-39. doi:10.1016/S0016-5085(03)00701-7.
23. Rosen T, Martinelli P. Erythema nodosum associated with infliximab therapy. *Dermatol Online J*. 2008;14(4):3.
24. Iborra M, Beltrán B, Bastida G, Aguas M, Nos P. Infliximab and adalimumab-induced psoriasis in Crohn's disease: a paradoxical side effect. *J Crohns Colitis*. 2011;5(2):157-161. doi:10.1016/j.crohns.2010.11.001.
25. Moran GW, Lim a WK, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. *Aliment*

Pharmacol Ther. 2013;38(9):1002-1024. doi:10.1111/apt.12491.

26. Guerra I, Pérez-Jeldres T, Iborra M, et al. Incidence, clinical characteristics, and management of psoriasis induced by Anti-TNF therapy in patients with inflammatory bowel disease: A nationwide cohort study. *Inflamm Bowel Dis.* 2016. doi:10.1097/MIB.0000000000000757.
27. Silverberg AVW authorRobyn SMAXWMSCNCHSS. Stricturing and Fistulizing Crohn's Disease Is Associated with Anti-tumor Necrosis Factor-Induced Psoriasis in Patients with Inflammatory Bowel Disease. *Dig Dis Sci.* 2018. doi:doi.org/10.1007/s10620-018-5096-2.
28. Blank MA, Ph D, Johannis J, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. 2012:1519-1528. doi:10.1056/NEJMoa1203572.
29. Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128. doi:10.1056/NEJMoa0810652.
30. Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by biological agents. A double-edged sword? *Autoimmun Rev.* 2010. doi:10.1016/j.autrev.2009.10.003.
31. Prinz JC. Autoimmune-like syndromes during TNF blockade: Does infection have a role? *Nat Rev Rheumatol.* 2011. doi:10.1038/nrrheum.2011.35.
32. Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology.* 2009. doi:10.1093/rheumatology/kep080.
33. Costa MF, Said NR, Zimmermann B. Drug-Induced Lupus due to Anti-Tumor Necrosis Factor α Agents. *Semin Arthritis Rheum.* 2008. doi:10.1016/j.semarthrit.2007.08.003.
34. Chung ES. Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor- α , in Patients With Moderate-to-

- Severe Heart Failure: Results of the Anti-TNF Therapy Against Congestive Heart failure
(ATTACH. *Circulation*. 2003;107(25):3133-3140.
doi:10.1161/01.CIR.0000077913.60364.D2.
35. Y.Sote, S.Green PM. Complete heart block after infliximab therapy. *Rheumatology*.
2008;47(2):227-228.
36. Lazzerini PE, Acampa M, Hammoud M, et al. Arrhythmic risk during acute infusion of
infliximab: A prospective, single-blind, placebo-controlled, crossover study in patients with
chronic arthritis. *J Rheumatol*. 2008;35(10):1958-1965.
37. Abedin M, Scheurich D, Reimold SC, Reimold AM. Acute coronary syndrome after infliximab
infusion. *Cardiol Rev*. 2006;14(1):50-52. doi:10.1097/01.crd.0000178320.51474.ac.
38. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after
therapy with a tumor necrosis factor antagonist. *AnnInternMed*. 2003;138(10):807-811.
39. Deepak P, Stobaugh DJ, Sherid M, Sifuentes H, Ehrenpreis ED. Neurological events with
tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration
Adverse Event Reporting System. *Aliment Pharmacol Ther*. 2013;38(4):388-396.
doi:10.1111/apt.12385.
40. Seror R, Richez C, Sordet C, et al. Pattern of demyelination occurring during anti-TNF- α
therapy: A french national survey. *Rheumatol (United Kingdom)*. 2013;52(5):868-874.
doi:10.1093/rheumatology/kes375.
41. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF- α Blockers. *Curr Neurol
Neurosci Rep*. 2017;17(4). doi:10.1007/s11910-017-0742-1.
42. Roach DR, Bean AGD, Demangel C, France MP, Briscoe H, Britton WJ. TNF Regulates
Chemokine Induction Essential for Cell Recruitment, Granuloma Formation, and Clearance
of Mycobacterial Infection. *J Immunol*. 2002;168(9):4620-4627.

doi:10.4049/jimmunol.168.9.4620.

43. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol*. 2006;2(11):602-610. doi:10.1038/ncprheum0336.
44. Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY. Risk for Overall Infection with Anti-TNF and Anti-integrin Agents Used in IBD: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis*. 2017;23(4):570-577. doi:10.1097/MIB.0000000000001049.
45. Wheat CL, Ko CW, Clark-Snustad K, Grembowski D, Thornton TA, Devine B. Inflammatory Bowel Disease (IBD) pharmacotherapy and the risk of serious infection: A systematic review and network meta-analysis. *BMC Gastroenterol*. 2017;17(1). doi:10.1186/s12876-017-0602-0.
46. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2016;375(20):1946-1960. doi:10.1056/NEJMoa1602773.
47. Wils P, Bouhnik Y, Michetti P, et al. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Aliment Pharmacol Ther*. 2018;47(5):588-595. doi:10.1111/apt.14487.
48. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(1):3-15. doi:10.1111/apt.14075.
49. Hanauer SB. Review article : safety of infliximab in clinical trials. *Aliment Pharmacol Ther*. 1999;13:16-22.
50. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DPM. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis

- patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2006;54(8):2368-2376. doi:10.1002/art.21978.
51. Slifman NR, Gershon SK, Lee J-H, Edwards ET, Braun MM. *Listeria monocytogenes* infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis Rheum.* 2003;48(2):319-324. doi:10.1002/art.10758.
52. FDA. Drugs FDA Drug Safety Communication : Drug labels for the Tumor Necrosis Factor - alpha (TNF α) blockers now include warnings about infection with *Legionella* and *Listeria* bacteria Facts about TNF α blockers. 2011:1-4.
53. Bodro M, Paterson DL. Listeriosis in patients receiving biologic therapies. *Eur J Clin Microbiol Infect Dis.* 2013;32(9):1225-1230. doi:10.1007/s10096-013-1873-1.
54. Lambertz ST, Nilsson C, Brådenmark A, et al. Prevalence and level of *Listeria monocytogenes* in ready-to-eat foods in Sweden 2010. *Int J Food Microbiol.* 2012. doi:10.1016/j.ijfoodmicro.2012.09.010.
55. Costard S, Espejo L, Groenendaal H, Zagmutt FJ. Outbreak-related disease burden associated with consumption of unpasteurized cow's milk and cheese, United States, 2009–2014. *Emerg Infect Dis.* 2017. doi:10.3201/eid2306.151603.
56. Tufariello JM, Chan J, Flynn JL. Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis.* 2003;3(9):578-590. doi:10.1016/S1473-3099(03)00741-2.
57. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis.* 2003;3(3):148-155. doi:10.1016/S1473-3099(03)00545-0.
58. Guidelines BTS. BTS recommendations for assessing risk and for managing *Mycobacterium*

- tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax*. 2005;60(10):800-805. doi:10.1136/thx.2005.046797.
59. Keane J, Gershon S, Wise RP, Mirabile-levens E, Kasznica J, Schwieterman WD, Siegel JN BM. Tuberculosis Associated With Infliximab ,. *N Engl J Med*. 2001;345(15):1098-1104.
60. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum*. 2005;52(10):2968-2974. doi:10.1002/art.21382.
61. Mariette X, Baron G, Tubach F, et al. Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy. *Ann Rheum Dis*. 2012. doi:10.1136/annrheumdis-2011-200408.
62. Edwards A, Gao Y, Allan RN, et al. Corticosteroids and infliximab impair the performance of interferon- γ release assays used for diagnosis of latent tuberculosis. *Thorax*. 2017.
63. Rutledge TF, Boyd MF, Mazurek M, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm reports Morb Mortal Wkly Rep Recomm reports / Centers Dis Control*. 2010;59(RR-5):1-25. doi:rr5415a4 [pii].
64. Group IBD. Evidence-based consensus on opportunistic infections in inflammatory bowel disease. *Intest Res*. 2018;16(2):178-193.
65. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis*. 2014;8(6):443-468. doi:10.1016/j.crohns.2013.12.013.
66. Ziakas PD, Mylonakis E. 4 Months of Rifampin Compared with 9 Months of Isoniazid for the Management of Latent Tuberculosis Infection: A Meta-analysis and Cost-Effectiveness Study That Focuses on Compliance and Liver Toxicity. *Clin Infect Dis*. 2009.

doi:10.1086/647944.

67. Park S-J, Jo K-W, Yoo B, et al. Comparison of LTBI treatment regimens for patients receiving anti-tumour necrosis factor therapy. *Int J Tuberc Lung Dis Off J Int Union Against Tuberc Lung Dis*. 2015. doi:10.5588/ijtld.14.0554.
68. Vonkeman H, ten Napel C, Rasker H, van de Laar M. Disseminated primary varicella infection during infliximab treatment. *J Rheumatol*. 2004;31(12):2517-2518.
69. Kopylov U, Levin A, Mendelson E, et al. Prior varicella zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: Implications for serological testing and vaccination guidelines. *Aliment Pharmacol Ther*. 2012. doi:10.1111/j.1365-2036.2012.05150.x.
70. Reich J, Wasan SK, Farraye FA. Vaccination and Health Maintenance Issues to Consider in Patients With Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2017.
71. Cullen G, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012. doi:10.1002/ibd.22950.
72. Gupta G, Lautenbach E, Lewis JD. Incidence and Risk Factors for Herpes Zoster Among Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2006. doi:10.1016/j.cgh.2006.09.019.
73. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013. doi:10.1111/apt.12182.
74. Department of Health. *Chapter 34: Varicella.*; 2012.
75. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention , diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis*. 2014;8(6):443-468. doi:10.1016/j.crohns.2013.12.013.

76. Guidotti LG, Ishikawa T, Hobbs M V., Matzke B, Schreiber R, Chisari F V. Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity*. 1996;4(1):25-36. doi:10.1016/S1074-7613(00)80295-2.
77. Wendling D, Auge B, Bettinger D, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthritis. *Ann Rheum Dis*. 2005;64(5):788-789. doi:10.1136/ard.2004.031187.
78. Charpin C, Guis S, Colson P, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. *Arthritis Res Ther*. 2009;11(6):R179. doi:10.1186/ar2868.
79. Doubrawa E, Augusto R, Ricca DM, et al. Use of infliximab in a patient with rheumatoid arthritis and chronic hepatitis B. 2012;52(4):50-52.
80. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut*. 2004;53(9):1363-1365. doi:10.1136/gut.2004.040675.
81. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. *Clin Mol Hepatol*. 2016. doi:10.3350/cmh.2016.0024.
82. Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2010;31(1):20-34. doi:10.1111/j.1365-2036.2009.04112.x.
83. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. *Ann Rheum Dis*. 2004;63 Suppl 2:ii18-ii24. doi:10.1136/ard.2004.028209.
84. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. *J Gastroenterol Hepatol*.

- 2006;21(9):1366-1371. doi:10.1111/j.1440-1746.2006.04559.x.
85. Fauci AS. Host factors and the pathogenesis of HIV-induced disease. *Nature*. 1996;384(6609):529-534. doi:10.1038/384529a0.
86. Poli G. Laureate ESCI award for excellence in clinical science 1999. Cytokines and the human immunodeficiency virus: From bench to bedside. *Eur J Clin Invest*. 1999;29(8):723-732. doi:10.1046/j.1365-2362.1999.00525.x.
87. T. H. Ho, R. Fausel, J. Torres, J. J. Yang, T. H. Swartz, J. A. Aberg, J.-F. Colombel SM. The effect of concurrent HIV-1 infection on the management of patients with inflammatory bowel disease. *J Crohns Colitis*. 2016;(supplement):S330.
88. Abreu C, Magro F, Vilas-Boas F, Lopes S, Macedo G, Sarmento A. Listeria infection in patients on anti-TNF treatment: report of two cases and review of the literature. *J Crohns Colitis*. 2013;7(2):175-182. doi:10.1016/j.crohns.2012.04.018.
89. Toruner M, Loftus E V., Harmsen WS, et al. Risk Factors for Opportunistic Infections in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2008;134(4):929-936. doi:10.1053/j.gastro.2008.01.012.
90. Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. *J Clin Rheumatol*. 2007;13(2):79-80. doi:10.1097/01.rhu.0000260411.75599.39.
91. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis*. 2008;67(5):710-712. doi:10.1136/ard.2007.081513.
92. George A. Stamatiades, Petros Ioannou GP and CT. Fungal infections in patients with inflammatory bowel disease: A systematic review. *Mycoses*. 2018;June(61(6)):366-376. doi:10.1111/myc.12753.

93. Roilides E, Dimitriadou-Georgiadou a, Sein T, Kaditsoglou I, Walsh TJ. Tumor necrosis factor alpha enhances antifungal activities of polymorphonuclear and mononuclear phagocytes against *Aspergillus fumigatus*. *Infect Immun*. 1998;66(12):5999-6003.
94. Warris A, Bjørneklett A GP. Invasive Pulmonary Aspergillosis Associated with Infliximab Therapy. *N Engl J Med*. 2001;344(14)(Apr 5):1099-1100.
95. Manz M, Beglinger C, Vavricka SR. Fatal invasive pulmonary aspergillosis associated with adalimumab therapy. *Gut*. 2009;58(1):149. doi:10.1136/gut.2008.161638.
96. Lee J-H, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum*. 2002;46(10):2565-2570. doi:10.1002/art.10583.
97. FDA. Drugs Information for Healthcare Professionals : Cimzia (certolizumab pegol), Enbrel (etanercept),. 2008:1-3.
98. D'Ovidio V, Vernia P, Gentile G, et al. Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFalpha therapy. *J Clin Virol*. 2008;43(2):180-183. doi:10.1016/j.jcv.2008.06.002.
99. Van Assche G, Vermeire S, Rutgeerts P. Management of acute severe ulcerative colitis. *Gut*. 2011;60(1):130-133. doi:10.1136/gut.2009.192765.
100. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. *J Crohn's Colitis*. 2013;7(1):1-33. doi:10.1016/j.crohns.2012.09.005.
101. Kopylov U, Sasson G, Geyshis B, et al. Cytomegalovirus positive ulcerative colitis: A single center experience and literature review. *World J Gastrointest Pathophysiol*. 2013;4(1):18-23. doi:10.4291/wjgp.v4.i1.18.
102. Kopylov U, Papamichael K, Katsanos K, et al. Impact of Infliximab and Cyclosporine on the

- Risk of Colectomy in Hospitalized Patients with Ulcerative Colitis Complicated by Cytomegalovirus - A Multicenter Retrospective Study. *Inflamm Bowel Dis*. 2017. doi:10.1097/MIB.0000000000001160.
103. Pillet S, Jarlot C, Courault M, et al. Infliximab does not worsen outcomes during flare-ups associated with cytomegalovirus infection in patients with ulcerative colitis. *Inflamm Bowel Dis*. 2015. doi:10.1097/MIB.0000000000000412.
104. Cotter TG, Gathaiya N, Catania J, et al. Low Risk of Pneumonia From Pneumocystis jirovecii Infection in Patients With Inflammatory Bowel Disease Receiving Immune Suppression. *Clin Gastroenterol Hepatol*. 2017. doi:10.1016/j.cgh.2016.11.037.
105. Kaur N, Mahl TC. Pneumocystis jirovecii (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci*. 2007;52(6):1481-1484. doi:10.1007/s10620-006-9250-x.
106. Sánchez-Tembleque MD, Corella C, Pérez-Calle JL. Vaccines and recommendations for their use in inflammatory bowel disease. *World J Gastroenterol*. 2013;19(9):1354-1358. doi:10.3748/wjg.v19.i9.1354.
107. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: Twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum*. 2002;46(12):3151-3158. doi:10.1002/art.10679.
108. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol*. 2005;32(11):2130-2135.
109. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295(19):2275-2285. doi:10.1001/jama.295.19.2275.
110. Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with

- tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf.* 2011;20(2):119-130. doi:10.1002/pds.2046.
111. Caspersen S, Elkjaer M, Riis L, et al. Infliximab for Inflammatory Bowel Disease in Denmark 1999-2005: Clinical Outcome and Follow-Up Evaluation of Malignancy and Mortality. *Clin Gastroenterol Hepatol.* 2008;6(11):1212-1217. doi:10.1016/j.cgh.2008.05.010.
112. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious Infections and Mortality in Association With Therapies for Crohn's Disease: TREAT Registry. *Clin Gastroenterol Hepatol.* 2006;4(5):621-630. doi:10.1016/j.cgh.2006.03.002.
113. Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. *Am J Gastroenterol.* 2014;109(2):212-223. doi:10.1038/ajg.2013.441.
114. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009. doi:10.1016/S0140-6736(09)61302-7.
115. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology.* 2011;141(5):1621-1628. doi:10.1053/j.gastro.2011.06.050.
116. Long MD, Herfarth HH, Pipkin C, Porter CQ, Sandler RS, Kappelman M. Increased Risk for Non-Melanoma Skin Cancer in Patients with Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2010;8(3):268-274. doi:10.1016/j.cgh.2009.11.024.Increased.
117. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology.* 2012. doi:10.1053/j.gastro.2012.05.004.

118. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA*. 2017;318(17):1679. doi:10.1001/jama.2017.16071.
119. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohn's Colitis*. 2010;4(5):511-522. doi:10.1016/j.crohns.2010.05.006.
120. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohn's Colitis*. 2010. doi:10.1016/j.crohns.2010.05.006.
121. Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(12):2146-2153. doi:10.1038/ajg.2011.283.
122. Siegel C a., Marden SM, Persing SM, Larson RJ, Sands BE. Risk of Lymphoma Associated With Combination Anti-Tumor Necrosis Factor and Immunomodulator Therapy for the Treatment of Crohn's Disease: A Meta-Analysis. *Clin Gastroenterol Hepatol*. 2009;7(8):874-881. doi:10.1016/j.cgh.2009.01.004.
123. Axelrad J, Bernheim O, Colombel JF, et al. Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol*. 2016. doi:10.1016/j.cgh.2015.07.037.
124. Shelton E, Laharie D, Scott FI, et al. Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. *Gastroenterology*. 2016. doi:10.1053/j.gastro.2016.03.037.
125. Annese V, Beaugerie L, Egan L, et al. European evidence-based consensus: Inflammatory bowel disease and malignancies. *J Crohn's Colitis*. 2015. doi:10.1093/ecco-jcc/jjv141.

For Peer Review

Review article: Managing the Adverse Events Caused by Anti-TNF Therapy in Inflammatory Bowel Disease

Shivaji UN^{1,2}, Sharratt CL^{5,6}, Thomas T⁴, Smith SCL³, Iacucci, M^{1,3}, Moran GW^{5,6}, Ghosh S^{1,3}, Bhala N^{4,7}

¹ National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre

² Institute of Immunology and Immunotherapy, University of Birmingham (UK)

³ Institute of Translational Medicine, Birmingham, UK

⁴ Department of Gastroenterology, University Hospitals Birmingham, UK

⁵ National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre

⁶ Nottingham Digestive Diseases Centre, Nottingham University Hospitals

⁷University of Birmingham, Birmingham, UK

Keywords: Crohn’s, Ulcerative Colitis, Infliximab, Adalimumab, Golimumab, Biologics, Anti-TNFα Complications, Adverse events

Corresponding Author:

Prof. Subrata Ghosh

Professor of Medicine

Director, Institute of Translational Medicine

University of Birmingham, Edgbaston. B15 2TH

United Kingdom

Office Phone: 0121 371 8026

Email: GhoshS@adf.bham.ac.uk

Shivaji,UN- literature search, evidence procurement, writing and editing manuscript, revision and approval

Sharratt,CL- literature search, evidence procurement, writing manuscript, revision and approval

Thomas,T- literature search and writing sections of manuscript, approval

Smith,SCL- editing manuscript, revision, approval

Iacucci,M- revision, critical review of manuscript, approval

Moran,GW- literature search, critical review of manuscript, revision, approval

Ghosh,S- Plan of this review, critical review of manuscript, revision, overall supervision and final approval

Bhala,N- critical review of manuscript, revision, overall supervision and final approval

For Peer Review

STRUCTURED SUMMARY

Background

Biological therapy is currently widely used to treat inflammatory bowel disease (IBD). Infliximab, adalimumab and golimumab are currently licensed anti-TNF therapies. Biosimilar anti-TNF monoclonal antibodies are increasingly used. Anti-TNF therapies are most widely used and their adverse effects are best characterised, which may cause significant morbidity and mortality in a small proportion of exposed patients. Gastroenterologists need to understand the mechanism for these effects, recognise these swiftly and manage such events appropriately.

Aim

This review aims to cover the range of potential adverse reactions as a result of biologic therapy and specifically management of these events.

Methods

A Medline and Pubmed search was undertaken. Search terms included were “anti-TNF”, “infliximab” or “adalimumab” or “golimumab” combined with the keywords “ulcerative colitis” or “Crohn’s disease” or “inflammatory bowel disease” and then narrowed to articles containing the keywords “complications”, “side effects” or “adverse events” or “safety profile”. International guidelines were also reviewed where relevant.

Results

Adverse events discussed in this review include infusion reactions, blood disorders and infections (including bacterial, viral, fungal and opportunistic infections) as well as autoimmune, dermatological disorders, cardiac and neurological conditions. Malignancies including solid organ, haematological, and those linked to viral disease are discussed.

Conclusions

Anti-TNF therapy has wide-ranging effects on the immune system resulting in a spectrum of potential adverse events in a small proportion of patients. Research advances are improving understanding, recognition and management of these adverse events.

INTRODUCTION

The use of biologics is currently approved for moderate-to-severe Crohn's disease (CD) and moderate to severe ulcerative colitis (UC)¹⁻⁹. Infliximab, adalimumab and golimumab are antibodies to tumour necrosis factor- α (TNF α). These drugs work on a common pathway of blocking TNF α , a pro-inflammatory cytokine closely linked to acute phase reaction and systemic inflammation, thereby reducing the degree of damage to tissues. These have been developed using different techniques therefore conferring different degrees of immunogenicity. [Infliximab (human-chimeric), adalimumab (fully human), golimumab (fully human), certolizumab (recombinant pegylated humanised Fab' fragment)].

These medications have transformed medical treatment options for inflammatory bowel disease (IBD) in recent years and are prescribed in increasing numbers. As there are less golimumab exposed patients than the other two anti-TNF monoclonal antibodies, less adverse effects have been reported but generally most adverse effects are class effects. Clinicians need to be aware of & recognise adverse events (AE/AEs) that may result from the use of these drugs and also have clear management strategies in different scenarios. This comprehensive review summarises a range of possible AEs providing evidence based guidance where available and pragmatic guidance for areas where evidence is lacking.

AIMS AND METHODS:

A MEDLINE and PUBMED search was undertaken by (U.S, C.L) for articles pertaining to adverse effects of anti-TNF therapy in IBD. After an initial title screen, all relevant articles were examined in full. The main aim of the review is to focus on management of adverse events caused by anti-TNF therapy. For clarity, these AEs are discussed in categories as per systems, alongside recommended course of action including any further investigations or management. Where relevant, this manuscript also refers to international guidelines.

Non-infectious complications and management strategies

Hypersensitivity reactions

Hypersensitivity reactions vary widely in presentation, ranging from acute infusion reactions to delayed hypersensitivity.

- Type I acute hypersensitivity reactions (IgE mediated) present as anaphylaxis
- Type II are cytotoxic; complement-mediated
- Type III are immune-complex related presenting as serum sickness
- Type IV are cell-mediated delayed hypersensitivity; mediated by T lymphocytes

Acute infusion reactions (IR) are defined as those which occur during or within 24 hours of the infusion. The symptoms vary and reactions can range from mild (flushing, dizziness, headache, itching, rash) to severe (anaphylactic-like)². Acute infusion reactions are relatively common, estimated to occur in up to 5% of infusions, with less than 1% of all infusions resulting in a severe reaction³.

Patients with antibodies to infliximab are at an increased risk of infusion reactions⁴ and case reports suggest hypersensitivity to adalimumab are also associated with adalimumab antibodies⁵. A review by the Food and Drug Administration (FDA) reported that injection site reactions were more common with adalimumab⁶ with higher reporting odds ratio(ROR) in the 20-29y age group (ROR=16.18). The ROR was seen to reduce with increasing age⁶. Injection site reactions to golimumab in the PURSUIT

study were low at 3.4% with no reported anaphylaxis or delayed hypersensitivity to 6 weeks⁷. Delayed reactions (24 hours to 14 days) presenting with arthralgia, myalgia, fever, fatigue and rash are much rarer (<1%)³. The pathophysiology of immunologic features are not completely understood⁸.

Management

The management of IRs is generally similar regardless of which agent has caused it. Typically, symptoms improve substantially or resolve completely after infusion rate adjustments and treatment with paracetamol, antihistamines or corticosteroids are provided. Evidence to support the use of premedication with corticosteroids or antihistamines is limited, with patients still experiencing infusion reactions despite pre-medication⁹ and therefore should be considered on an individual basis. Injection site pain due to adalimumab can be reduced by using low volume formulations which are free from citrate buffers, with no change in efficacy¹⁰.

In severe acute reactions, it is recommended that infusion is stopped and focus should be on maintaining airway, circulation as per standard anaphylaxis guidelines¹¹. (Table 1) Delayed infusion reactions are typically managed by antihistamines, paracetamol and corticosteroids. A systematic review looked at management of infusion reactions and presented useful algorithms to manage mild, moderate and severe reactions¹². These algorithms are simple, and a pragmatic tool to use for the vast majority of reactions seen in clinical practice¹². After a hypersensitivity reaction, it is pragmatic to obtain therapeutic drug levels and anti-drug antibody levels.

Table 1- Hypersensitivity reactions to anti-TNF therapy

Complication	Diagnosis	Management Strategy
Type 1 Hypersensitivity This is more common when antibody titres are high. Incidence is higher during re-introduction of drugs	<ul style="list-style-type: none">Clinical diagnosisSerum mast cell tryptaseDetection of antibodies on serum analysis where available	<ol style="list-style-type: none">Mild reactions: Slow infusion ratesConsider hydrocortisone injections as a pre-administration medicationAnaphylaxis reactions: Treat as per ALS pathway with adrenaline, steroids and anti-histamines
Type 2 Complement Mediated Non-specific symptoms	<ul style="list-style-type: none">Detection of antibodies on serum analysis where available	<ol style="list-style-type: none">Symptomatic treatmentConsider stopping treatment
Type 3 Immune-Complex Mediated Serum sickness	<ul style="list-style-type: none">Difficult to detect on assays, immune complexes known to adhere to membranes	<ol style="list-style-type: none">Symptomatic treatmentConsider stopping the drug and switch if antibodies are confirmed
Type 4 T-Cell Mediated Delayed hypersensitivity reaction (after 24 hours up to 14 days post-infusion).	<ul style="list-style-type: none">Clinical diagnosis	<ol style="list-style-type: none">Symptomatic managementConsider stopping drug

Anti – TNF: Anti-Tumour Necrosis Factor; ALS: Advanced Life Support

Haematological effects

Leucopenia

Neutropenia has been reported in anti-TNF α treatment-exposed patients, with up to 20% of patients developing neutropenia on at least one occasion¹³. TNF α up-regulates other pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor, involved in the differentiation and maturation of haematopoietic progenitor cells¹⁴. TNF α blockade could mediate bone marrow failure by inhibiting stem cell differentiation¹⁵. However, the reduction in neutrophil count following TNF α inhibitor therapy is not seen for other cells from the same lineage (myeloid progenitor cell), specifically basophils, eosinophils and monocytes. The risk of neutropenia is significantly higher in patients with a low baseline neutrophil count or a previous history of neutropenia^{13,16}.

Thrombocytopenia

Isolated thrombocytopenia following the use of anti-TNF drugs^{17,18} has been reported. There are multiple hypotheses as to the possible aetiology, including autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes triggering the complement cascade, another unknown autoimmune mechanism, or idiosyncratic reaction¹⁸.

Anaemia

Anaemia is considered a marker of active disease in IBD and therefore clinicians need to first consider this as an aetiology. The incidence and prevalence of anaemia was approximately 19% and 28% respectively, in a recent population based cohort study. Crohn's with stricturing disease and long-standing UC were recognised as risk factors¹⁹. One study showed only marginal improvement in anaemia after treatment with anti-TNF therapy suggesting that disease activity in itself has a major role to play²⁰.

In this section, anaemia directly attributable to biologics is discussed, which is rare. There are sporadic case reports of aplastic anaemia with infliximab, more commonly in patients with rheumatoid arthritis than IBD²¹. A single case of infliximab induced autoimmune haemolytic anaemia (in a patient found to be anti-nuclear antibody (ANA) positive 1:40) has also been reported²².

Management of haematological effects

All patients starting anti-TNF therapy should have a baseline complete blood count with repeat testing every three to six months. At the onset of neutropenia, the anti-TNF should be withheld if the neutrophil count is deemed too low by the clinician. The patient should be left drug-free until neutrophil counts recover & anti-TNF therapy restarted when deemed clinically safe. Neutropenia can occur in patients managed with combination therapy with an anti-metabolite and this should be borne in mind and should be discontinued first. A neutrophil count less than 1000/mm³ should raise concern and <500/mm³ should lead to discontinuation of incriminating drugs and close monitoring. Rare anti-TNF induced systemic lupus erythematosus should be excluded and sargramostim is rarely necessary after drug discontinuation.

Thrombocytopenia can be managed by drug cessation, corticosteroid therapy or rescue therapy with intravenous immunoglobulin (IVIG). Thrombocytopenia has been reported to be prolonged after cessation of therapy. In severe cases this could persist for up to 6 months and also preclude exposure to any further anti-TNF agents¹⁸. This is likely to be a class effect and re-challenge with same class could be risky and therefore discouraged¹⁷. In severe cases, specialist haematology input is suggested.

Anaemia in IBD is more commonly seen due to ongoing disease activity. Clinicians should first consider assessment for disease and strategies to control and manage anaemia secondary to disease as per guidelines. As anaemia related only to therapy is rare, there is no specific guidance in current literature regarding future therapy with anti-TNF. Cessation of therapy would depend on

careful physician-patient discussion taking into account the severity of anaemia and alternative treatment strategies. Involving haematologist in refractory cases would be prudent. (Table 2)

For Peer Review

Table 2- Haematological complications with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Leucopenia	<ul style="list-style-type: none">Blood count monitoring	1. If < safety threshold: stop drug, monitor blood count
Neutropenia		2. Restart drug when counts are within normal range
		3. Monitor
		4. Consider G-CSF
Thrombocytopenia	<ul style="list-style-type: none">Blood count monitoringEstablish temporal relationship to drugSecondary cases of low platelets to be excluded including concomitant drug therapy	1. If < safety threshold: stop drug, monitor platelet count
Anaemia	<ul style="list-style-type: none">Blood count monitoringBone marrow aspiration in refractory cases	2. Consider IV immunoglobulins & steroids
Drug related anaemia is rare but aplastic anaemia can be serious		3. Consider switching to different class of biologic
		1. If aplastic anemia: withdraw and stop drug
		2. Refractory cases warrant specialist hematology assessment

G-CSF- Granulocyte-Colony Stimulating Factor

Dermatological effects

In addition to skin malignancies anti-TNF therapy can cause a wide range of dermatological conditions. Most notably they include local skin irritation or reaction, increased skin infection rates, psoriasis, eczema, acne, and alopecia. Other rare dermatological complications include erythema nodosum²³, granuloma annulare and interstitial granulomatous dermatitis. Although some of the above complications are also seen as extra-intestinal manifestations of disease, temporal association with biologic therapy should help differentiate disease related complications from drug related complications.

Psoriasis and psoriasiform reactions can occur directly as a result of anti-TNF α therapy, which interestingly is used by dermatologists to treat severe cases of psoriasis. Psoriasis is a relatively common side effect of anti-TNF α therapy, with 1.5-5% of patients developing this manifestation²⁴. It is seen most commonly in females, typically 2-6 months following initiation of therapy²⁵. A nationwide cohort study reported incidence rates of anti-TNF induced psoriasis in IBD at 0.5% per patient-year²⁶. A more recent study shows a much higher incidence at 10.5%²⁷, but psoriasiform lesions are more common than psoriasis and have distinctive features. According to current evidence, females, smokers and patients with fistulising disease appear to be at risk²⁷. In addition to anti-TNF α induced psoriasis, psoriasiform and drug-induced psoriasiform lesions have been well recognised. Psoriasiform drug reactions can be distinguished histologically from psoriasis and resolve swiftly on cessation of drug therapy. Re-challenge results in recurrence of the lesions. The psoriasiform lesions could be secondary to infections and resolve on its treatment, though the infective origin of these are not always clear nor are their implications²⁵.

The exact mechanism triggering de novo psoriasis is unclear, although it has been postulated to be secondary to increased cutaneous expression of interferon alpha (IFN α). IFN α is released from dendritic cells to recruit T cells and pro-inflammatory cytokines IL-12 and IL-23. TNF α would

normally block IFN α expression and so anti-TNF α results in up regulation of IFN α ²⁴. Higher levels of IFN are seen in anti-TNF α induced psoriasis than idiopathic psoriasis²⁵.

Management

Management of psoriasis due to anti-TNF α depends on severity of symptoms. Milder cases of psoriasis can be treated clinically with topical therapy without cessation of anti-TNF, however more severe cases may require anti-TNF α withdrawal²⁴. About 80% of patients respond to a combined approach of steroids and biologics withdrawal²⁶. The use of another anti-TNF α agent may result in recurrence of psoriasis in majority of cases (52%)²⁵. Ustekinumab has been used in the treatment of CD²⁸ and psoriasis²⁹. There have been rare reports of paradoxical worsening of psoriasis with ustekinumab but not known to cause drug-induced psoriasis²¹. Ustekinumab is potentially an attractive option for treatment of refractory anti-TNF α induced psoriasis²⁵ requiring withdrawal of primary drug. Methotrexate has been used but does not appear to be effective in all cases²⁶. It is a useful option to have in selected cases. (Table 3)

Table 3- Dermatological adverse effects with anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Psoriasis Relatively Common (1.5% - 5% of patients on anti-TNFs)	<ul style="list-style-type: none"> Clinical diagnosis Histology of skin lesions Establish temporal relationship between initiation of biologic therapy and development of psoriasis 	<ol style="list-style-type: none"> Specialist involvement from dermatology In mild cases: topical steroid therapy In severe cases: stop drug and consider alternatives such as Methotrexate Ustekinumab for managing both conditions is a viable alternative
Psoriasiform lesions Common	<ul style="list-style-type: none"> Clinical Diagnosis Consider skin infections causing the rash 	<ol style="list-style-type: none"> Consider stopping drug in severe cases. Responds well to cessation of drug therapy Treat skin infection as appropriate
Erythema Nodosum Granuloma Annulare Interstitial Granulomatous Dermatitis Very rare	<ul style="list-style-type: none"> Clinical Diagnosis 	<ol style="list-style-type: none"> No clear evidence on management as these conditions are rare Specialist dermatology involvement is advised Usually not necessary to withhold or stop drug Clinician decision based on risk: benefit assessment

Anti – TNF : Anti-Tumour Necrosis Factor ;

Autoimmune-like disorders

Autoimmune-like disorders/syndromes are a group of conditions observed in patients on anti-TNF therapy. This was first described in initial studies of infliximab in patients with rheumatoid arthritis³⁰.

These disorders include a variety of conditions such as positive antibodies e.g. –anti-nuclear antibodies, anti-double stranded DNA antibodies (dsDNA) (commonly IgM type), on immunological testing, various systemic or organ-specific autoimmune diseases as documented in the BIOGEAS registry, drug-induced systemic lupus erythematosus (DIL) called lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optical neuritis & inflammatory ocular disease, multiple sclerosis (MS)-like central nervous system (CNS) demyelination and peripheral neuropathies³¹.

William et al described anti-TNF α induced lupus (ATIL) based on the severity of symptoms displayed and suggested that ATIL is a distinct syndrome in itself³² and are likely to be different from drug induced lupus. In a pooled analysis across various diseases, studies which included patients with IBD showed that whilst ANA positivity was very common after anti-TNF therapy (40%-56%), asymptomatic anti-nuclear antibodies or anti-double stranded DNA antibodies require observation but not discontinuation of anti-TNF. The full range of symptoms of ATIL was seen in only about <1% of patients³². Most patients with full blown ATIL had fever, rash, arthritis and haematological abnormalities.

A large case series was reported by Costa et al comparing drug-induced lupus secondary to anti-TNF and classic drug-induced lupus³³. Both groups had similar systemic features and symptoms but there were some features that distinguished one group from the other. 72% of patients with anti-TNF drug-induced lupus had cutaneous manifestations compared to about 25% in classic drug-induced lupus group. Classic drug-induced lupus was not usually associated with antibodies to dsDNA and extractable nuclear antigen (ENA) or with complement consumption. 90% of anti-TNF α

1 drug-induced lupus patients were positive for anti-dsDNA antibodies and >50% had anti-extractable
2 nuclear antigen antibodies and decreased serum complement levels³³.
3
4
5
6
7
8

9 *Management*

10
11
12 The management of autoimmune-like disorders/syndromes secondary to anti-TNF therapy requires
13 a customised therapeutic approach according to severity of the induced autoimmune disease. ATIL
14 should be considered a distinct condition and managed accordingly. There are features which could
15 help distinguish this. The incidence/prevalence of dsDNA antibodies and hypocomplementaemia is
16 greater in ATIL, whilst anti-histone antibodies, the hallmark of classic drug-induced lupus, are less
17 commonly found³².
18
19
20
21
22
23
24
25
26

27 In patients with a positive ANA, it is not in itself an indication for discontinuation of therapy. In the
28 presence of mild features, cessation of therapy is probably sufficient. However, it can be continued
29 in patients with isolated cutaneous lesions or immunological alterations in whom biologics are
30 thought to be essential to treat underlying disease, with closer follow-up. In patients with involvement
31 of internal organs (kidney, lungs, nervous system), cessation of therapy is mandatory with addition
32 of corticosteroids and/or immunosuppressive agents^{30,33}. After discontinuation of the incriminating
33 anti-TNF the prognosis is generally very favourable. The presence of diagnosed SLE is a
34 contraindication to anti-TNF exposure.
35
36
37
38
39
40
41
42
43
44
45

46 **Cardiac effects**

47
48
49 It was reported that worsening cardiac failure was a possible adverse event in a randomised
50 controlled trial investigating the use of anti-TNF therapy in cardiac failure³⁴. Majority of patients
51 enrolled were New York Heart Association III (NYHA) at baseline and the group receiving high dose
52 infliximab (10 mg/kg) were adversely affected with an increased likelihood of hospitalization, high
53
54
55
56
57
58
59
60

frequency of worsening heart failure, with the risk of adverse clinical events persisting for up to five months after cessation of therapy³⁴. The exact mechanism of heart failure with anti-TNF α use remains unclear.

There have been case reports of second degree and complete heart block after infliximab therapy but are rare³⁵. This is more likely to happen in rheumatological conditions as there may be underlying cardiac involvement. A single blind prospective study which included rheumatological conditions concluded that new-onset cardiac arrhythmias, particularly ventricular tachyarrhythmia, developed during infliximab infusion, but their incidence did not achieve statistical significance³⁶. Acute coronary syndrome following infusion has been reported but this too is very rare³⁷. The rarer cardiac effects are based on reports with a very small number of patients, mostly from the rheumatology cohort who are at higher risk of having cardiac disorders.

Management

Current guidance recommends that use of anti-TNF therapy is best avoided in those with NYHA III/IV heart failure³⁸. All patients who develop heart failure while on an anti-TNF agent should discontinue therapy, conventional medication for treatment of heart failure started and specialty advice sought. An alternate class of agent should be considered for the primary disease process. It is still unclear whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYHA class I/II) ³⁸. For patients commencing anti-TNF therapy who have specific cardiac risk factors such as hypertension, valve disorders or ischemic heart disease, our recommendation is that clinicians should get a baseline electrocardiogram to record QT interval among other features and clinically assess the patient for any features of pre-existing heart failure that may preclude therapy. Not all studies have substantiated an association of anti-TNF therapy with heart failure and this is rare in patients with IBD.

Table 4- Cardiac adverse effects with anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Cardiac Failure	<ul style="list-style-type: none"> Clinical diagnosis Objective assessments with investigations 	<ol style="list-style-type: none"> Avoid anti-TNFs in NYHA III and IV heart failure If drug precipitates heart failure: stop the drug Treat for heart failure with diuretics and early specialist involvement Switch to another class of drugs
Second and third-degree Heart Block More commonly seen in the treatment of rheumatological conditions; less so with IBD	<ul style="list-style-type: none"> 12 Lead ECG Cardiac monitoring 	<ol style="list-style-type: none"> Monitor patients for features of decompensation Specialist involvement for further management Stop drug and switch to another class
Arrhythmias More commonly seen in the treatment of rheumatological conditions; less so with IBD	<ul style="list-style-type: none"> 12 Lead ECG Cardiac monitoring 	<ol style="list-style-type: none"> Usually transient and does not need any specific management If transient episodes are self-limiting: consider continuing drug If persistent: seek specialist cardiology opinion

Anti – TNF : Anti-Tumour Necrosis Factor; NYHA- New York Heart Association

1 **Neurological effects**

2
3
4 *Demyelination*

5
6
7 Demyelination has been recognised as a complication of anti-TNF therapy. A review of FDA
8
9 adverse event recording system showed that among 772 reports of neurological complications, 18%
10
11 of patients had IBD. About 36% of patients had received infliximab and peripheral neuropathy was
12
13 the most commonly reported event³⁹. Demyelination can occur in central or peripheral nervous
14
15 systems⁴⁰. It is unclear as to whether the relationship is truly causal, or whether anti-TNF triggers
16
17 an existing tendency for demyelination.
18
19

20
21
22 *Management*

23
24
25 The patients who have a family history of demyelination disorders may be at higher risk and this
26
27 should be considered before the therapeutic agent is chosen⁴¹. It is standard guidance to avoid anti-
28
29 TNF therapy in patients with concomitant multiple sclerosis or history of optic neuritis. In patients
30
31 who develop neurological deterioration and suspected demyelination during therapy, treatment with
32
33 biologic agent should be discontinued⁴¹ and specialist neurology opinion should be sought. The
34
35 clear relationship between demyelinating events and anti-TNF can be difficult to establish as IBD
36
37 may also be associated with demyelination. Treatment with corticosteroids, IVIG and
38
39 plasmapheresis are rarely necessary. (Table 5)
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 5- Neurological reactions with anti-TNF therapy

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Demyelination	<ul style="list-style-type: none"> Clinical diagnosis Nerve Conduction Studies MRI 	<ol style="list-style-type: none"> 1. Stop drug and consider alternatives 2. Seek specialist Neurology involvement 3. Consider pulse therapy with high dose methylprednisolone 4. Consider IV Immunoglobulin

MRI-Magnetic resonance imaging

Infections and management strategies

Biologics are strong immunosuppressive agents and can increase risk of infection depending on their mechanism of action. TNF α is essential for activation, differentiation and recruitment of several immunological cell types; it has a role in granuloma formation, maintenance of granuloma integrity⁴² and host response to mycobacteria and intracellular organisms⁴³. A recent meta-analysis found that anti-TNF therapy was associated with a greater infection risk than placebo in treating UC but anti-integrin therapy was not; neither class showed an increased infection risk over placebo in CD⁴⁴. Other studies have confirmed increased risk in both forms of IBD.

A recent systematic review by Wheat et al concluded that at present there is no evidence of a higher odds of serious infection from the newly available biologic therapies such as vedolizumab and ustekinumab compared to anti-TNFs⁴⁵. Feagan et al report that infections in patients exposed to ustekinumab for CD is no higher than placebo in UNITI trials⁴⁶ and Wils et al reported 1 serious pulmonary infection in a cohort of 122 ustekinumab patients, followed up over 2 years⁴⁷. Bye et al reported an increased risk of Clostridium difficile infection with vedolizumab therapy but concomitant steroid and narcotic analgesics were identified as risk factors⁴⁸.

Bacterial infections

Patients receiving anti-TNF therapy have been reported to acquire both common and uncommon bacterial infections. Common sites for infection include upper and lower respiratory tracts, skin and subcutaneous tissue, urinary tract and GI tract⁴⁹.

Management

Common infections are treated with oral antibiotics as per local guidelines. A pragmatic approach would be to have a lower threshold to start treatment and switch to intravenous drugs in the presence of systemic symptoms. In severe sepsis requiring prolonged antimicrobial treatment, anti-TNF

therapy may have to be withheld. Restarting therapy can be considered once patients are afebrile, white cell counts within normal range and relevant imaging (CT, MRI pelvis) show no evidence of infective source. (Table 6)

Uncommon infections

Several non-mycobacterial intracellular infections, including listeriosis caused by *Listeria monocytogenes* and legionnaires' disease most often caused by *Legionella pneumophila*, have been associated with anti-TNF therapy⁵⁰. Listeria sepsis and meningitis has been described in patients receiving anti-TNF drugs⁵¹ and in 2011, the FDA added a boxed warning about the risk of listeriosis and legionnaires' disease for the entire class of TNF α inhibitors⁵². There are a few case reports of listeriosis complicating anti-TNF therapy. Listeriosis carries significant mortality, therefore requiring prompt diagnosis and aggressive treatment. The risk appears to be higher during the first year of therapy⁵³. Anti-TNF should be discontinued till the patient recovers from listeriosis.

Management

Suspicion of infection requires confirmatory testing and treatment using standard antibiotic regimes depending on pathogen isolated. Listeriosis is more likely to be seen in patients consuming mould-ripened cheese regardless of whether it is from pasteurised or unpasteurised milk and also from cold smoked gravad fish⁵⁴. In one study from USA, unpasteurised milk and dairy products were noted to significantly increase the risk of infections caused by *E-coli*, *Salmonella* and *Campylobacter*⁵⁵. In view of this overall increased risk of infections, it is safer for patients to avoid consumption of unpasteurised milk whilst on anti-TNF drugs.

Mycobacteria and tuberculosis

Tuberculosis (TB) caused by mycobacterium bacilli is a serious infection which carries significant morbidity. TNF α is necessary for a Th1-based cell-mediated immune response important in

activating macrophages to kill intracellular mycobacteria, and limit spread by formation of granulomas^{56,57}. The majority of exposed immunocompetent hosts have latent TB (LTB) which can subsequently lead to reactivation of infection if there is compromise to the immune system, such as initiation of anti-TNF drugs⁵⁸. It is therefore critical to identify and treat LTB prior to starting anti-TNF therapy⁵⁸.

An association between anti-TNF therapy and development of TB was noted when the FDA MedWatch spontaneous reporting system demonstrated 70 TB cases in a median of 12 weeks after initial infliximab exposure, in 2001⁵⁹⁻⁶⁸. Both extra-pulmonary and disseminated TB are more common in patients treated with anti-TNF therapy, compared with immunocompetent patients⁵⁹⁻⁶⁰. It has been hypothesised that the early occurrence of TB after infliximab may suggest reactivation of LTB rather than a de novo infection⁶⁰. Due to the high risk of reactivation, screening for TB is recommended prior to starting anti-TNF α .

The diagnosis of LTB can be difficult and should include a combination of detailed history and supportive investigations. At present, IGRA (interferon gamma release assay) and TST (tuberculin skin test) are commonly used in most centres. In a study by Mariette et al which looked at how effective the available tests are, it was noted that when one of the IGRA tests replaced TST, it influenced the decision made by physicians, leading to 28% fewer patients receiving anti-TB (ATB) prophylaxis⁶¹. This is likely because IGRA tests are more specific. As per this study, IGRA does not appear to be affected by corticosteroid or immunosuppressant therapy⁶¹. However, this may not always be the case as shown in an *ex vivo* study in which corticosteroids and infliximab reduced the performance of IGRA⁶². At present, IGRA is possibly more reliable than the other options available. TST is less specific and can be less frequently positive due to corticosteroid or immunosuppressant therapy and this should be borne in mind. Based on their findings, Mariette et al proposed the an algorithm for assessing patient, which is now generally applied prior to starting anti-TNF α therapy⁶¹. All patients should undergo appropriate history +/- chest x-ray. For those with a positive history or

1 x-ray, treat with ATB prophylaxis. For those with negative history, check with IGRA test (authors
2 recommend GOLD, followed by T-SPOT if indeterminate). Those with negative results require no
3 further screening. Those with positive results require ATB prophylaxis. Patients with indeterminate
4 GOLD and T-SPOT test should undergo TST testing. Negative results require no further action, but
5 a positive TST should be treated with prophylaxis⁶¹.
6
7
8
9
10

11
12 In patients who have a positive TST and negative IGRA, the degree of clinical suspicion should
13 guide management, based on history and chest x-ray with a very low threshold to treat the patient.
14 Generally, performing both TST and IGRA is not recommended. An initial indeterminate borderline
15 IGRA can be followed up with TST and if the latter is positive the patient should be treated. The
16 CDC recommend testing with either IGRA or TST, but a combination of both may be appropriate
17 where clinical suspicion of LTB is high, or risk of subsequent LTB reactivation may result in a poorer
18 outcome (such as those on immunosuppressants)⁶³.
19
20
21
22
23
24
25
26
27
28
29

30 *Management*

31
32 Guidelines by European Crohn's and Colitis organisation (ECCO)²⁶ and British Thoracic Society
33 (BTS)⁵⁸ on screening and management of TB are similar in principle, suggesting treatment of LTB
34 prior to initiation of anti-TNF therapy with a complete therapeutic regimen. If there is clinical
35 suspicion +/- radiographic changes suggestive of TB, patients should be referred for treatment of
36 LTB⁵⁸. Other patients should undergo LTB screening tests. The optimal screening strategy for these
37 patients is still debatable.
38
39
40
41
42
43
44
45

46 After diagnosis of latent TB in a patient with IBD, appropriate treatment should be administered for
47 at least 3 weeks prior to commencement of anti-TNF therapy^{64,65} ; however if treatment with anti-
48 TNF therapy is considered very urgent simultaneous treatment for latent TB and IBD may be
49 considered. Alternative therapies such as vedolizumab or ustekinumab may also be considered for
50 UC or CD. Short latent TB therapies are increasingly considered such as rifampicin for 4 months or
51 isoniazid plus rifampicin for 3 months as adherence to 9 months of daily isoniazid poses
52
53
54
55
56
57
58
59
60

1 challenges^{66,67}. Exposure to active TB during anti-TNF therapy should lead to prompt re-evaluation
2
3 for latent or active TB. In case of active TB, anti-TNF should be discontinued and active TB treated.
4
5 If absolutely necessary, anti-TNF may be resumed after at least 2 months of anti-TB therapy with
6
7 satisfactory response, though it may sometimes be resumed earlier if absolutely necessary.
8
9 Increasingly other monoclonal antibodies such as ustekinumab or vedolizumab are being
10
11 considered. Annual re-testing for LTB in patients on anti-TNF therapy depends on risk factors for
12
13 exposure to TB and desirable in geographical areas with endemic TB. (Table 6)
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

<u>Complication</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
<i>Common bacterial infections</i>		
Respiratory Tract	<ul style="list-style-type: none">• Clinical diagnosis• Relevant investigations depending on symptoms	1. Appropriate antibiotics based on site of infection
Urinary Tract		2. Consider early therapy
Gastrointestinal		3. If any signs of sepsis: stop drug
Cellulitis		4. Restart biologics when good evidence of resolved infection. (WCC, imaging)
<i>Serious Bacterial Infections:</i>		
Listeriosis	<ul style="list-style-type: none">• Serology• CT/MRI of brain• Lumbar puncture if meningitis suspected	1. Appropriate antibiotics based on sensitivity
Legionnaires' disease		2. Seek specialist microbiology advice
Septic Arthritis		
Septicemia		
<i>Tuberculosis (TB):</i>		
Latent TB Re-Activation	<ul style="list-style-type: none">• Risk assessment based on initial screening with Quantiferon or T-Spot Testing• Thorough history and risk factor assessment• Chest X-Ray	<ol style="list-style-type: none">1. If positive or indeterminate: involve specialists2. Treat as per ECCO guidelines and British Thoracic Society Guidelines3. Risk: Benefit analysis by clinician4. Consider alternative therapy i.e. vedolizumab or ustekinumab

WCC-white cell count

Viral infections

A majority of human viral infections are self-limiting but some are capable of causing chronic infection [e.g. human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)]. There are viruses linked to malignancy, such as Epstein-Barr virus (EBV) and human papilloma virus (HPV). EBV will be discussed in more detail in 'malignancy' section of this text.

Varicella (VZV) and Shingles

This can present with severe or disseminated disease if contracted while on anti-TNF therapy⁶⁸. In one study, the prevalence of prior varicella zoster virus (VZV) infection among IBD patients was greater than 90%⁶⁹ and it was not noted that a significant number had a VZV IgG negative status. It is known that patients with IBD are at a higher risk of VZV infection and more so when on immunosuppressive therapy^{70,71}.

Herpes zoster or shingles is caused by reactivation of VZV. The incidence of shingles is again increased in patients with IBD, the elderly population at particular risk. In a study looking at herpes zoster in IBD, it was seen that patients with CD were at higher risk; age >45 years, treatment with corticosteroids for >2 weeks, thiopurine therapy were associated with increased risk of infection⁷². Long et al reported similar findings and also noted that patients on anti-TNF therapy for IBD are at higher risk of herpes zoster with an odds ratio of 1.81 (95% CI: 1.48-2.21)⁷³.

Management

Immunocompromised patients exposed to VZV should be treated with VZV immunoglobulin⁷⁴. Patients who contract VZV or shingles during a period of immunosuppression require antiviral therapy. If oral therapy is appropriate, valganciclovir should be considered as this provides higher oral bioavailability than aciclovir⁷⁵. (Table 7)

Prevention of infection is possible due to availability of effective vaccines. It is recommended that all patients are screened for evidence of past infection prior to starting biologics or immunosuppressives including steroids. ECCO suggest that in seronegative patients two-dose course of varicella vaccine should be given at least 3 weeks prior to commencement of therapy⁶⁵. If subsequent immunisation is necessary, it can be administered after a 3–6 month cessation of all immunosuppressives as both the VZV and shingles vaccines are live vaccines⁷⁵, although there is emerging evidence that administration of live zoster vaccine to patients already on anti-TNF therapy did not result in disease and there was expected immune response to the vaccine⁷³.

Hepatitis B

TNF α and interferon (IFN) γ are released by cytotoxic T lymphocytes on antigen recognition of the hepatitis B virus (HBV), activating two viricidal pathways, plus antigen non-specific T cells & macrophages⁷⁶. Reactivation of HBV may occur during anti-TNF therapy, or on subsequent withdrawal (secondary to immune reconstitution). Reactivation of chronic HBV carriers (hepatitis B surface antigen (HBsAg) positive, undetectable HBV DNA, normal LFTs) after anti-TNF therapy has been reported⁷⁷. Patients who have had HBsAg seroconversion following exposure to HBV [HBsAg negative, anti-HBc (core antibody) positive and anti-HBsAg antibody positive] have been successfully treated with anti-TNF therapy without HBV reactivation during follow up⁷⁸. Chronic active HBV patients already successfully controlled with antiviral therapy prior to introduction of anti-TNF show no deterioration in the viral load or liver enzymes^{79,80}. A comprehensive review by Pattullo⁸¹ looked at incidence & prevalence of HBV reactivation in IBD when treated with immunosuppressants without HBV prophylaxis; risk stratification of patients was also done based on type of biologic therapy⁸¹. The incidence of immunosuppression related HBV reactivation was noted to be about 36% in HBsAg positive patients. The overall prevalence of HBV in IBD ranged from 0.6-17% for HBsAg positive patients, and 1.6-42% for HBsAg negative/anti-HBc positive

patients. The risk estimate of HBV reactivation was reported to be moderate (1-10%) with anti-TNF⁸¹.

Management

All patients should be screened prior to initiation of therapy, although which patients should receive antiviral therapy remains unclear. Screening should be carried out checking for hepatitis B surface antigen, antibody to surface antigen & anti HB core antibody levels and if HBsAg or anti-HBc is positive, DNA quantification should be done⁶⁵. Chronic HBV carriers and those with HbsAg seroconversion should be considered for antiviral therapy and hepatology involvement. It is recommended that patients who are due to start biologics (moderate risk) are given anti-viral prophylaxis if they are HBsAg positive and continued for at least 6 months after completion of immunosuppressive therapy⁸¹. In case of reactivation, it is recommended that one of the antivirals is started and continued for at least 6 to 12 months after immunosuppressive therapy has been stopped. The antiviral medication of choice may depend on the patient's individual circumstances, and the planned duration of immunosuppression⁸². Entecavir and tenofovir are now preferred antivirals in IBD patients due to their rapid onset of action, highest anti-viral potency with low incidence of resistance⁶⁵. Whilst lamivudine is used, this has its limitations if long term therapy is required, as resistance can occur in up to 30% of patients after 1 year and 70% after 5 years⁸². Peginterferon-alpha-2a (IFN α) is best avoided due to the risk of myelosuppression and also risk of exacerbating CD⁶⁵.

Hepatitis C

TNF α appears to be involved in the pathogenesis of HCV, with patients with higher serum TNF α levels less likely to respond to anti-viral therapy⁸³. TNF α blockade may increase reactivity of peripheral T cells to antigen stimulation⁸³. Biologics have an acceptable safety profile for use in patients with HCV and is not contraindicated in concomitant HCV infection. However, in the

presence of acute HCV, anti-TNF therapy is contraindicated⁸⁴. In the presence of chronic HCV, the decision to treat with anti-TNF depends on liver synthetic function. It is best avoided in patients who are Child-Pugh category B or C⁸⁴. HCV patients being treated with anti-TNF therapy should have close monitoring of aminotransferases with consideration for discontinuation of treatment with continued elevations⁸³. The guidelines from ECCO suggest cautious use of antivirals due to drug interactions⁶⁵. Infection diagnosed whilst on anti-TNF therapy does not necessarily require cessation of therapy⁶⁵. There is no data yet on the use of newer antivirals for HCV in the context of biologics use for IBD but there are no contraindications for their concurrent use.

Management

The ECCO guidelines are equivocal about screening for HCV prior to use of immunosuppressive therapy⁶⁵. However, it would be prudent to screen patients who are likely to need biologics considering the high curative rates with newer anti-viral drugs for HCV. All patients with HCV infection should be discussed and managed jointly with hepatology services, especially when biologics are indicated for IBD. During the course of therapy, close monitoring of liver functions is key.

HIV infection

The interaction between TNF α and the human immunodeficiency virus (HIV) has been the subject of much scrutiny. The molecular pathway by which HIV expression is upregulated by TNF α is well described^{85,86}. Despite these findings, use of anti-TNF in HIV-patients must be balanced with a potential increase in the risk of opportunistic infections in patients with an attenuated immune system.

The evidence base for advice regarding use of biologics in patients with HIV and IBD is limited. Within a cohort study and several case reports, biologic therapy with infliximab in refractory IBD patients has been demonstrated to be effective in inducing disease remission with only a minority

experiencing adverse effects⁸⁷⁻⁷⁷. It is important to note that initial CD4+ count in patients included in these studies are > 200 cells/mL. The ECCO guidelines⁶⁵ also suggest that the HIV-IBD cohort of patients are less predisposed to infection on highly active anti-retroviral therapy (HAART) than if they did not receive HAART. In this cohort, adverse effects have presented as either a pre-disposition to infections, deranged CD4+ count or HIV viral loads.

Abreu et al describe an HIV positive, thiopurine-intolerant patient treated with IFX for a UC-flare unresponsive to steroids⁸⁸ who had been on ART (emtricitabine/tenofovir/efavirenz) with undetectable HIV viral load & CD4+ count of 357/mm³ prior to infliximab therapy. Although excellent disease response was achieved, he was diagnosed with listeriosis and was successfully treated. (CD4+ count 350/mm³). Infliximab was restarted with no clinical consequences. It is likely these patients with IBD remain at increased risk of opportunistic infections⁸⁹.

Other examples of adverse effects of biologics in HIV are reported in the rheumatology cohort⁹⁰. In one case series⁹¹, a patient who was not on HAART therapy was observed to have an increase in viral load (22,148 c/ml to 428,503 c/ml) following initiation of infliximab therapy. This required temporary cessation of infliximab and the rise was not observed at re-administration.

Within the limited evidence available, it is noted that patients do benefit from adequate disease response with no specific HIV-related complications. Due to risk of AEs, it is recommended that screening for HIV is undertaken prior to treatment with biologics and patients with IBD recognised as HIV positive are managed by a multi-specialty team. Generally, in the absence of other infections treatment of HIV infected patients with anti-TNF is relatively safe. This group of patients must ideally be on HAART. A discussion about potential increased risk of infection, baseline blood tests including CD4+ count (ideally 200 cells/mL+), and HIV viral load is necessary. Close monitoring throughout duration of therapy is key. An Increase in HIV viral load needs discussion with specialists and discontinuation of biologic may become necessary. Any overt sign of infection merits hospital

admission to identify and treat the infection source and biologics paused. Restarting biologics should be discussed based on clinical aspects of each case. (Table 7)

For Peer Review

Table 7- Viral infections in the use of anti-TNF therapy

Complication	Diagnosis	Management Strategy
Varicella Relatively common	<ul style="list-style-type: none">Clinical diagnosisSerology testing available	<ol style="list-style-type: none">Treat with varicella immunoglobulinAntimicrobial therapy with valganciclovir
Chronic Stable HBV Reactivation of chronic infection	<ul style="list-style-type: none">Screening for HBV mandatoryClose monitoring of liver function and viral load	<ol style="list-style-type: none">Joint care with HepatologistMay require treatment with antiviralsBiologics can be continued unless acute fulminant liver failure suspected
Chronic Active HBV on antiviral therapy	<ul style="list-style-type: none">Screening for HBV mandatoryClose monitoring of liver function and viral load	<ol style="list-style-type: none">Continue antiviralsEntecavir and tenofovir drugs of choice
Hepatitis C	<ul style="list-style-type: none">Screening for HCV recommended prior to anti-TNF therapyClose monitoring of LFTs and HCV RNA load in HCV infected patients	<ol style="list-style-type: none">Joint care with HepatologistContinue biologic with close monitoringNo contraindication for therapy
Cytomegalovirus (CMV)	<ul style="list-style-type: none">Check serology for CMV IgM and viral PCRSupported by tissue diagnosis with histology and immunohistochemistry	<ol style="list-style-type: none">Treatment with IV ganciclovir and switch to oral valganciclovir for total of 2-3 weeksUse foscarnet as per sensitivitiesIf systemic CMV infection: consider stopping anti-TNF
Human Immunodeficiency Virus	<ul style="list-style-type: none">Close monitoring in addition to CD4+ counts	<ol style="list-style-type: none">Continue biologics when HAART established and CD4+ counts are above 350Consider withholding biologic when CD4+ <200Joint care with multidisciplinary decision approach

Anti – TNF : Anti-Tumour Necrosis Factor ; HBV-Hepatitis B virus; HCV-Hepatitis C virus; LFTs- liver function tests; PCR- polymerase chain reaction; HAART- highly active antiretroviral therapy

For Peer Review

Fungal infections

Patients with IBD are known to be at an increased risk of fungal infections. This is due to multiple factors such as severity of disease activity, comorbidities, treatment with opioids, surgery, poor nutritional status, leucopenia and older age⁹². Another factor is immunosuppressive therapy, important of which are anti-TNFs. A risk factor analysis by one recent systematic review reported anti-TNF therapy as the predominant factor associated with fungal infections⁹².

Aspergillosis

Aspergillosis, caused by *Aspergillus fumigatus* is a serious pulmonary infection which warrants prompt diagnosis and treatment. Attenuation of the inflammatory pathway through TNF α blockade alters the cytotoxic immune response to fungal infections and in aspergillosis, it is involved in polymorphonuclear leucocyte activation in response to infection⁹³. The evidence is mostly from case reports. In 2001, a case of invasive pulmonary aspergillosis was reported in a patient with CD on anti-TNF therapy⁹⁴. There have been other case reports since but overall, it appears to be a rare occurrence. This usually presents initially with a poorly productive cough and can progress to respiratory insufficiency; radiological changes are seen⁹⁴⁻⁹⁵.

Management

The definitive diagnosis is on culture of broncho-alveolar fluid. The infection is treated with prolonged anti-fungal therapy based on sensitivities; amphotericin B or voriconazole or caspofungin is used. The condition carries very poor prognosis. Concomitant tuberculous cavity needs exclusion. (Table 8)

Histoplasmosis

This is another potential opportunistic infection reported in patients exposed to anti-TNF treatment. In a case series of ten immunocompromised subjects from an area endemic with histoplasmosis, 9

contracted histoplasmosis shortly after commencing infliximab infusions. Clinical presentation can be varied and include pulmonary, extra-pulmonary or disseminated disease symptoms which are non-specific⁹⁶.

Table 8- Fungal infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Candidiasis Commonly localised infections but systemic and invasive infection can be life threatening	<ul style="list-style-type: none"> Serology, culture and molecular studies 	1. Localised infections: Topical therapy 2. Invasive infections: <ol style="list-style-type: none"> Stop biologic IV Fluconazole Seek specialist advice
Aspergillosis Pulmonary symptoms and invasive infection	<ul style="list-style-type: none"> Serology, culture and imaging 	1. Stop biologics 2. IV Anti-fungal therapy (Consider IV voriconazole) 3. Caspofungin is another option 4. Specialist involvement
Histoplasmosis Usually pulmonary infection	<ul style="list-style-type: none"> Serology, culture and radiology 	1. Stop biologic therapy 2. Treatment with either one of: <ol style="list-style-type: none"> Amphotericin B initially and step-down therapy to an azole preparation Itraconazole
Pneumocystis Jirovecii	<ul style="list-style-type: none"> Clinical diagnosis Culture, microscopic and molecular diagnosis 	1. Co-trimoxazole 960mg BD, if severe infection increases to 1.44 g BD 2. Specialist involvement

Management

Invasive fungal infections should be treated with systemic antifungals and all immunosuppressant medication should be reviewed. The FDA in 2008 have issued post market drug safety information alerting healthcare providers that invasive fungal infections and histoplasmosis in patients receiving anti-TNF drugs are not being swiftly recognised, resulting in possible delays to patient therapy. The FDA recommends the involvement of infectious diseases specialists⁹⁷ in the management of such cases. (Table 8)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Other Opportunistic infections

Cytomegalovirus (CMV)

CMV infection (detected by serology) could be due to reactivation of latent infection during immunomodulator or biologic therapy, but usually is itself mild or asymptomatic even on immunosuppressants. However, CMV colitis, retinitis, pneumonia or severe CMV infection during treatment of IBD requires further assessment⁷⁵ to plan management. Nevertheless, not all cases of CMV infection in anti-TNF use progress to CMV disease⁹⁸.

The diagnosis of CMV disease using histopathology with immunohistochemistry is highly sensitive and specific. This combined with CMV viral load (CMV DNA detected by PCR in serum & tissues) can provide most information about disease state⁷⁵. CMV viral loads of >250 copies/mg is a predictor for patients presenting with corticosteroid-resistant disease⁷⁵.

CMV disease manifesting as colitis is a recognised complication of IBD and should be screened for in those patients presenting with acute severe colitis⁹⁹. Typically, patients may have had previous exposure to immunosuppressive therapy and experienced prolonged corticosteroid therapy or corticosteroid-refractory disease. CMV can also be a cause of chronic pouchitis¹⁰⁰.

Management

It is important that diagnosis is established swiftly. When considered as a differential diagnosis, testing for CMV viral load with PCR is recommended to look for CMV disease especially in ill patients with systemic manifestations. Histology and immunohistochemistry may be used to support the diagnosis of CMV colitis. Once diagnosed, ECCO recommend a 2-3 week course of ganciclovir therapy for CMV disease, and immunosuppressants are withheld⁷⁵. However, a retrospective cohort case study of CMV-positive colitides, identified that patients with milder colitis were less likely to be treated, and could respond to standard immunosuppressive therapy without additional treatment for

CMV. CMV may be transiently reactivated and disappear without antiviral therapy. In one study it was noted that those with more severe disease were more likely to be treated with ganciclovir, and were more likely to require either rescue therapy or surgery, despite adequate treatment of CMV¹⁰¹. CMV colitis complicating UC leading to acute severe colitis can be challenging to manage. A study by Kopylov et al reported that the outcomes for patients with severe colitis. Patients received infliximab/ciclosporin with ganciclovir vs ganciclovir alone, and they had similar colectomy rates¹⁰². In patients who test positive for CMV whilst on anti-TNF therapy, there is a evidence that anti-TNF can be continued¹⁰³. (Table 7)

Pneumocystis pneumonia (PCP) or pneumocystis jirovecii pneumonia (PJP)

This is a serious infection reported in patients after use of immunosuppressants. A large population based cohort study looked at risk of PJP in IBD patients¹⁰⁴. Although there is some evidence that the overall hazard risk of PJP in IBD is higher than normal population, the absolute risk of PJP is considered to be very low (0.03% in their cohort)¹⁰⁴. In a large case series of PJP after infliximab use, mean onset of symptoms reported was 21 days although majority of patients were exposed to concomitant immunosuppressive therapy. Over a quarter (27%) of patients died¹⁰⁵ in these reported series, so early recognition and therapy is paramount. ECCO guidance recommends that patients on triple immunotherapy with one being a calcineurin inhibitor or anti-TNF should receive standard prophylaxis with Trimethoprim-sulfamethoxazole (co-trimoxazole) if tolerated. It should be considered in those on dual immunosuppression especially if one is a calcineurin inhibitor⁷⁵ and in anti-TNF regimens with associated corticosteroid use⁷⁵. However, pill-burden and side effects are to be kept in mind. Co-trimoxazole is an effective option for prophylaxis and active infection. Clinicians should discuss with their local microbiology and infectious disease departments. Although more recent studies report very low risk, clinicians have to be vigilant throughout the course of treatment and decision on prophylaxis has to be on a case-by-case basis. (Table 8)

Infection prevention and vaccination recommendations

The main focus of the article is on management of adverse effects and our stress on prevention though very important, is limited as these have been extensively addressed in ECCO guidelines. ECCO guidance recommends that prior to immunosuppression a detailed history and examination including prior bacterial, viral and fungal infections, particularly herpes, VZV, TB exposure, prolonged travel/stay or plans to travel to TB endemic or tropical areas and completion of childhood vaccination programmes. Further advice should include cervical smear screening for women, food hygiene and avoidance of raw and unpasteurised foods. Education on safe use and preparation of dairy & meat products can benefit patients at risk of *Listeria* infection whilst on anti-TNF α therapy. Live attenuated vaccines must be avoided on immunomodulator or anti-TNF therapy and ideally patients should receive annual inactivated influenza vaccine and pneumococcal vaccine as required. Prior to the onset of immunosuppression, consider vaccination with any outstanding routine vaccines plus HBV, VZV (if seronegative and no clinical history) and HPV⁷⁵. If patients require live vaccines during therapy, the risk: benefit assessment of vaccination should be undertaken. Patients are usually immunocompetent within 3-12 months¹⁰⁶ after cessation of therapy. Corticosteroid therapy alone is not considered to cause significant immunocompromise unless high doses (20mg or higher) have been used continuously for more than two weeks¹⁰⁶.

Malignancy

Malignancies thought to be linked to immunosuppressive agents and anti-TNF use include solid organ malignancies, non-melanoma skin cancer (NMSC), melanoma, lymphoproliferative malignancies, and those with viral association such as EBV-related lymphomas and HPV-related cervical cancers or dysplasia. However, difficulty remains in establishing a cause-effect relationship.

A possible association between anti-TNF use and malignancy first arose from post-marketing reports to the FDA. There were 26 cases of lymphoma reported in patients with rheumatoid arthritis or CD disease treated with etanercept or infliximab¹⁰⁷. Further studies demonstrated an increased risk for solid organ and NMSC in patients treated with anti-TNF and further immunosuppressive therapies¹⁰⁸. Many IBD patients are either on multidrug regimes or have had past exposure to thiopurines (or other immunosuppressants) prior to anti-TNF usage.

Historically most trial data is from the rheumatology population. A meta-analysis derived from nine clinical trials of patients receiving anti-TNF treatment or placebo identified a number needed to harm of 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months¹⁰⁹. The malignancy rates were significantly more common in those treated with higher doses ($\geq 6\text{mg/kg}$ of infliximab every 8 weeks or 40mg of adalimumab alternate weeks)¹⁰⁹. A more recent meta-analysis of 74 randomised controlled trials concerning adalimumab and infliximab showed no overall relative risk (RR) increase on short term follow up for malignancy with the exception of NMSC which had a RR of 2.02 (95% CI 1.11-3.95)¹¹⁰. A 6-year follow up study from the national Danish registers only identified three solid organ malignancies and one case of melanoma, with total follow up ranging from 0.1-72.1 months¹¹¹. The Crohn's therapy, resource, evaluation and assessment tool (TREAT) registry is collecting prospective data on large number of CD patients to evaluate the long-term safety of CD therapies. Data published from the registry in 2006 showed mortality rates to be similar

between infliximab and non-infliximab patient groups after a short period of follow up (mean follow up 1.9 years)¹¹². Subsequent data from the registry published in 2014 (with follow up of up to 7.6 years) has shown that none of immunosuppressants, infliximab or combination therapy to be an independent risk factor for malignancy¹¹³. However, the follow-up period remains short and future analysis of the registry is likely to provide further evidence.

The CESAME Study Group¹¹⁴ assessed the impact of thiopurine use on development of NMSC— comprised of basal cell carcinoma, squamous cell carcinoma and lymphoproliferative disorders (increased risk found in the thiopurine group). Although a large number of patients were included, the risk of malignancy secondary to biologics could not be assessed due to relatively small number of patients on these drugs¹¹⁵. A study by Long et al published in 2010 assessed risk of malignancy and concluded that IBD in itself increased risk of NMSC (incidence rate ratio IRR 1.64 95% CI 1.51-1.78) and a nested case-control model showed an increased risk because of recent biologic use among patients with CD (adjusted OR 2.07, 95% CI 1.28–3.33)¹¹⁶; patients on combination therapy had the highest OR compared to medication-free patients (OR 5.85 95%CI 3.2-10.8)¹¹⁶. Another study in 2012 reported that patients were at higher risk of melanoma when exposed to biologics and NMSCs were mainly related to thiopurine therapy¹¹⁷. The most recent French national cohort study showed an increased risk of lymphoma in treatment exposed patients. When compared with unexposed patients, the risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR, 2.60; 95% CI, 1.96-3.44; P < 0.001), anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60-3.64; P < 0.001), or combination therapy (aHR, 6.11; 95% CI, 3.46-10.8; P < 0.001)¹¹⁸.

There remains concern about cases of hepatosplenic T-cell lymphoma (HSTCL) (a rare and aggressive form of non-Hodgkin's lymphoma affecting predominantly young men) occurring following infliximab, adalimumab or thiopurine use. In a study published by Thai et al, they reported 22 cases of HSTCL in IBD and most were associated with thiopurine therapy either as monotherapy or in combination with anti-TNF. Whilst a link is recognised, quantifying this risk to individual patients

on current evidence is difficult¹¹⁹. They also concluded that despite the risk, benefits of treatment far outweighed the risks¹²⁰.

Secondly, observational studies have noted a potential predisposition to development of EBV related lymphoproliferative disorders in IBD patients, in particular those treated with thiopurines and anti-TNF α agents⁷⁵. Patients with EBV are predisposed to post-transplant lymphoproliferative disorders (PTLD), where T-cell immune surveillance is impaired⁷⁵. EBV related lymphomas may present in the gut, rather than nodal sites. Screening for EBV should ideally be considered, however there is no current vaccination for EBV naïve patients. In those developing EBV on therapy, treatment with antiviral medication and withdrawal of therapy should be considered⁷⁵. IBD itself does not appear to increase risk of lymphoma diagnosis¹²¹. However use of a thiopurine for IBD or combination therapy with an anti-TNF α may increase risk¹²¹. Establishing any isolated effect of anti-TNF α on lymphoma development is challenging. In a meta-analysis looking at lymphoma rates in CD patients treated with anti-TNF α , two thirds of all patients were also receiving immunomodulator therapies¹²²; anti-TNF α treated patients appeared to have an increased risk of lymphoma (SIR 3.23 95% CI 1.5-6.9) compared to the expected population rate¹²². The SIR was also increased when compared to previously studied patients on immunomodulator therapy alone (1.7 95% CI 0.5-7.1), however this did not reach statistical significance¹²². There were too few patients treated with isolated anti-TNF therapy to determine the individual risk of anti-TNF usage on lymphoma development¹²².

Management principles in malignancy

The association between various malignancies and anti-TNF treatment remains unclear, but it is important that patients' history of previous or pre-existing cancer is carefully documented prior to initiation of biologic treatment. The use of biologics as monotherapy can be considered in patients with previous history of cancer. Axelrad et al noted that at 5 years after prior cancer diagnosis no significant difference in cancer free survival could be demonstrated between IBD treatment with anti-

TNF monotherapy, immunosuppressant monotherapy, anti-TNF combined with thiopurine therapy, though numerically anti-TNF monotherapy had the least cancer recurrence¹²³. In a meta-analysis of 16 studies of immune mediated diseases, including 8 studies involving IBD patients, similar rates of cancer recurrence were observed among individuals affected by previous cancer who received no immunosuppressives, anti-TNF monotherapy, immunosuppressant therapy or combination therapies¹²⁴. Therefore, in patients with a history of cancer, recent or past, effective therapy for IBD can be used after consideration of risks & benefits and discussion with oncologists. ECCO guidelines also provide advice on managing IBD patients with previous history of malignancy¹²⁵. Generally, among biologics, monotherapy anti-TNF α , vedolizumab or ustekinumab may all be used, but often thiopurines are avoided.

Table 9- Malignancies with anti-TNF therapy

<u>Complication</u>	<u>Causative drug/s</u>	<u>Diagnosis</u>	<u>Management Strategy</u>
Melanoma	Anti-TNF	<ul style="list-style-type: none"> Clinical diagnosis Skin biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Non-melanoma skin cancer	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Clinical diagnosis Skin biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Lymphoma <ul style="list-style-type: none"> HSTCL PTLD 	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Cross sectional imaging Tissue Biopsy 	<ol style="list-style-type: none"> 1. Stop drug 2. Consider switching drug class
Other malignancies: Leukoencephalopathy	Dual Anti-TNF + thiopurine therapy	<ul style="list-style-type: none"> Clinical diagnosis Imaging Tissue Biopsy 	<ol style="list-style-type: none"> 1. Stop the drug 2. Consider switching drug class 3. Relevant Specialist involvement

Anti – TNF : Anti-Tumour Necrosis Factor ; HSTCL: Hepatosplenic T-cell Lymphoma; PTLD: Post-transplant lymphoproliferative disorder

CONCLUSION

The use of biologics is now standard therapy for IBD used either as monotherapy or in combination with immunomodulators. A review of safety data of currently used biologics show cumulative evidence for anti-TNF α as they have been used for longer duration. In summary, acute infusion reactions are common with anti-TNF, neutropenia is a worrying AE and may require temporary cessation of therapy. Infections are significantly higher with anti-TNF which include common and uncommon bacterial infections, mycobacterial infections (in particular TB), viral and fungal infections and opportunistic pathogens. Diagnostic and management strategies are outlined in separate tables.

Anti-TNF therapy causes a wide range of dermatological presentations. It is important to differentiate drug induced psoriasis from psoriasiform rash. Treatment may range from topical therapy to anti-TNF α withdrawal. Ustekinumab may be useful in these cases.

Malignancies thought to be linked to anti-TNF use include solid organ malignancies, NMSC, melanoma, lymphoproliferative malignancies, and those with a viral association. However, difficulty remains in attributing a causal relationship particularly given the confounding of thiopurine use. The link between HSTCL is recognised but currently not quantified due to scarcity of data. IBD increases risk for NMSC, with the risk further increased for in combination therapy. The risk of lymphoma is increased with combination therapy with thiopurines including EBV related lymphoma but it is to be noted that results from the TREAT registry suggest that none of the immunosuppressants, infliximab or combination therapy are an independent risk factor for malignancy. However, the follow up duration remains short. Biologics can be used in patients with prior history of cancer after careful discussion about risks and benefits with oncologists.

1 Finally, although these therapies are often very effective, they present unique challenges. It is likely
2 that in the future biologics will be used in a wider cohort of patients earlier in their disease journey,
3 and therefore prompt recognition of adverse events secondary to drugs is important. Further
4 reporting of rarer AEs and prompt recording of common AEs in registries will help assess risk more
5 accurately. This information should help clinicians inform their patients of risks associated with each
6 therapy and will lead to more informed decision making, thus improving patient care.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

REFERENCES

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance therapy for Ulcerative Colitis. *N Engl J Med*. 2005;353:2462-2476.
2. Wee JS, Petrof G, Jackson K, Barker JNWN, Smith CH. Infliximab for the treatment of psoriasis in the U.K.: 9 years' experience of infusion reactions at a single centre. *Br J Dermatol*. 2012;167(2):411-416. doi:10.1111/j.1365-2133.2012.10931.x.
3. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol*. 2003;98(6):1315-1324. doi:10.1111/j.1572-0241.2003.07457.x.
4. Ricart E, Panaccione R, Loftus E V, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol*. 2001;96(3):722-729. doi:10.1111/j.1572-0241.2001.03612.x.
5. Steenholdt C, Svenson M, Bendtzen K, Thomsen OØ, Brynskov J, Ainsworth MA. Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease. *J Crohns Colitis*. 2012;6(1):108-111. doi:10.1016/j.crohns.2011.08.001.
6. Matsui T, Umetsu R, Kato Y, et al. Age-related trends in injection site reaction incidence induced by the tumor necrosis factor- α (TNF- α) inhibitors etanercept and adalimumab: The Food and Drug Administration adverse event reporting system, 2004–2015. *Int J Med Sci*. 2017. doi:10.7150/ijms.17025.
7. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):96-109.e1. doi:10.1053/j.gastro.2013.06.010.
8. Duburque C, Lelong J, Iacob R, et al. Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. *Aliment Pharmacol Ther*.

- 2006;24(5):851-858. doi:10.1111/j.1365-2036.2006.03026.x.
9. Colombel J-F, Loftus E V., Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo Clinic experience in 500 patients. *Gastroenterology*. 2004;126(1):19-31. doi:10.1053/j.gastro.2003.10.047.
10. Nash P, Vanhoof J, Hall S, et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis. *Rheumatol Ther*. 2016. doi:10.1007/s40744-016-0041-3.
11. Truhlář A, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Section 4. Cardiac arrest in special circumstances. *Resuscitation*. 2015;95:148-201. doi:10.1016/j.resuscitation.2015.07.017.
12. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-Related Infusion Reactions: Systematic Review. *J Crohns Colitis*. 2015. doi:10.1093/ecco-jcc/jjv096.
13. Hastings R, Ding T, Butt S, et al. Neutropenia in patients receiving anti-tumor necrosis factor therapy. *Arthritis Care Res (Hoboken)*. 2010;62(6):764-769. doi:10.1002/acr.20037.
14. Beutler BA. The role of tumor necrosis factor in health and disease. *J Rheumatol Suppl*. 1999;57:16-21.
15. Keystone EC. Tumor necrosis factor-alpha blockade in the treatment of rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001;27(2):427-443.
16. Sebastian S, Ashton K, Houston Y, Diggory TM, Dore P. Anti-TNF therapy induced immune neutropenia in Crohns disease- report of 2 cases and review of literature. *J Crohns Colitis*. 2012;6(6):713-716. doi:10.1016/j.crohns.2012.01.014.
17. Salar A, Bessa X, Muñiz E, Monfort D, Besses C, Andreu M. Infliximab and adalimumab-induced thrombocytopenia in a woman with colonic Crohn's disease [7]. *Gut*. 2007;56(8):1169-1170. doi:10.1136/gut.2007.123547.

18. Casanova MJ, Chaparro M, Martínez S, Vicuña I, Gisbert JP. Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease. *J Crohns Colitis*. 2012;6(10):1034-1037. doi:10.1016/j.crohns.2012.04.001.
19. Eriksson C, Henriksson I, Brus O, et al. Incidence, prevalence and clinical outcome of anaemia in inflammatory bowel disease: a population-based cohort study. *Aliment Pharmacol Ther*. 2018. doi:10.1111/apt.14920.
20. Ioannis E. Koutroubakis, MD, Claudia Ramos–Rivers, MD, Miguel Regueiro, MD, Efstratios Koutroumpakis, MD, Benjamin Click, MD, Marc Schwartz, MD, Jason Swoger, MD, Leonard Baidoo, MD, Jana G. Hashash, MD, Arthur Barrie, MD, Michael A. Dunn, MD, and David G M. The influence of anti-TNF agents on hemoglobin levels of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(7):1587-1593.
21. Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Van Assche G. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther*. 2012;36(4):312-323. doi:10.1111/j.1365-2036.2012.05189.x.
22. Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor α treatment in Crohn's disease: a prospective cohort study. *Gastroenterology*. 2003;125(1):32-39. doi:10.1016/S0016-5085(03)00701-7.
23. Rosen T, Martinelli P. Erythema nodosum associated with infliximab therapy. *Dermatol Online J*. 2008;14(4):3.
24. Iborra M, Beltrán B, Bastida G, Aguas M, Nos P. Infliximab and adalimumab-induced psoriasis in Crohn's disease: a paradoxical side effect. *J Crohns Colitis*. 2011;5(2):157-161. doi:10.1016/j.crohns.2010.11.001.
25. Moran GW, Lim a WK, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. *Aliment*

Pharmacol Ther. 2013;38(9):1002-1024. doi:10.1111/apt.12491.

26. Guerra I, Pérez-Jeldres T, Iborra M, et al. Incidence, clinical characteristics, and management of psoriasis induced by Anti-TNF therapy in patients with inflammatory bowel disease: A nationwide cohort study. *Inflamm Bowel Dis.* 2016. doi:10.1097/MIB.0000000000000757.
27. Silverberg AVW authorRobyn SMAXWMSCNCHSS. Stricturing and Fistulizing Crohn's Disease Is Associated with Anti-tumor Necrosis Factor-Induced Psoriasis in Patients with Inflammatory Bowel Disease. *Dig Dis Sci.* 2018. doi:doi.org/10.1007/s10620-018-5096-2.
28. Blank MA, Ph D, Johannis J, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. 2012:1519-1528. doi:10.1056/NEJMoa1203572.
29. Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128. doi:10.1056/NEJMoa0810652.
30. Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by biological agents. A double-edged sword? *Autoimmun Rev.* 2010. doi:10.1016/j.autrev.2009.10.003.
31. Prinz JC. Autoimmune-like syndromes during TNF blockade: Does infection have a role? *Nat Rev Rheumatol.* 2011. doi:10.1038/nrrheum.2011.35.
32. Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology.* 2009. doi:10.1093/rheumatology/kep080.
33. Costa MF, Said NR, Zimmermann B. Drug-Induced Lupus due to Anti-Tumor Necrosis Factor α Agents. *Semin Arthritis Rheum.* 2008. doi:10.1016/j.semarthrit.2007.08.003.
34. Chung ES. Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor- α , in Patients With Moderate-to-

- Severe Heart Failure: Results of the Anti-TNF Therapy Against Congestive Heart failure
(ATTACH. *Circulation*. 2003;107(25):3133-3140.
doi:10.1161/01.CIR.0000077913.60364.D2.
35. Y.Sote, S.Green PM. Complete heart block after infliximab therapy. *Rheumatology*. 2008;47(2):227-228.
36. Lazzerini PE, Acampa M, Hammoud M, et al. Arrhythmic risk during acute infusion of infliximab: A prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. *J Rheumatol*. 2008;35(10):1958-1965.
37. Abedin M, Scheurich D, Reimold SC, Reimold AM. Acute coronary syndrome after infliximab infusion. *Cardiol Rev*. 2006;14(1):50-52. doi:10.1097/01.crd.0000178320.51474.ac.
38. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *AnnInternMed*. 2003;138(10):807-811.
39. Deepak P, Stobaugh DJ, Sherid M, Sifuentes H, Ehrenpreis ED. Neurological events with tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration Adverse Event Reporting System. *Aliment Pharmacol Ther*. 2013;38(4):388-396. doi:10.1111/apt.12385.
40. Seror R, Richez C, Sordet C, et al. Pattern of demyelination occurring during anti-TNF- α therapy: A french national survey. *Rheumatol (United Kingdom)*. 2013;52(5):868-874. doi:10.1093/rheumatology/kes375.
41. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF- α Blockers. *Curr Neurol Neurosci Rep*. 2017;17(4). doi:10.1007/s11910-017-0742-1.
42. Roach DR, Bean AGD, Demangel C, France MP, Briscoe H, Britton WJ. TNF Regulates Chemokine Induction Essential for Cell Recruitment, Granuloma Formation, and Clearance of Mycobacterial Infection. *J Immunol*. 2002;168(9):4620-4627.

doi:10.4049/jimmunol.168.9.4620.

43. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol*. 2006;2(11):602-610. doi:10.1038/ncprheum0336.
44. Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY. Risk for Overall Infection with Anti-TNF and Anti-integrin Agents Used in IBD: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis*. 2017;23(4):570-577. doi:10.1097/MIB.0000000000001049.
45. Wheat CL, Ko CW, Clark-Snustad K, Grembowski D, Thornton TA, Devine B. Inflammatory Bowel Disease (IBD) pharmacotherapy and the risk of serious infection: A systematic review and network meta-analysis. *BMC Gastroenterol*. 2017;17(1). doi:10.1186/s12876-017-0602-0.
46. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2016;375(20):1946-1960. doi:10.1056/NEJMoa1602773.
47. Wils P, Bouhnik Y, Michetti P, et al. Long-term efficacy and safety of ustekinumab in 122 refractory Crohn's disease patients: a multicentre experience. *Aliment Pharmacol Ther*. 2018;47(5):588-595. doi:10.1111/apt.14487.
48. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(1):3-15. doi:10.1111/apt.14075.
49. Hanauer SB. Review article : safety of infliximab in clinical trials. *Aliment Pharmacol Ther*. 1999;13:16-22.
50. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DPM. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis

- patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2006;54(8):2368-2376. doi:10.1002/art.21978.
51. Slifman NR, Gershon SK, Lee J-H, Edwards ET, Braun MM. *Listeria monocytogenes* infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis Rheum.* 2003;48(2):319-324. doi:10.1002/art.10758.
52. FDA. Drugs FDA Drug Safety Communication : Drug labels for the Tumor Necrosis Factor - alpha (TNF α) blockers now include warnings about infection with *Legionella* and *Listeria* bacteria Facts about TNF α blockers. 2011:1-4.
53. Bodro M, Paterson DL. Listeriosis in patients receiving biologic therapies. *Eur J Clin Microbiol Infect Dis.* 2013;32(9):1225-1230. doi:10.1007/s10096-013-1873-1.
54. Lambertz ST, Nilsson C, Brådenmark A, et al. Prevalence and level of *Listeria monocytogenes* in ready-to-eat foods in Sweden 2010. *Int J Food Microbiol.* 2012. doi:10.1016/j.ijfoodmicro.2012.09.010.
55. Costard S, Espejo L, Groenendaal H, Zagmutt FJ. Outbreak-related disease burden associated with consumption of unpasteurized cow's milk and cheese, United States, 2009–2014. *Emerg Infect Dis.* 2017. doi:10.3201/eid2306.151603.
56. Tufariello JM, Chan J, Flynn JL. Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis.* 2003;3(9):578-590. doi:10.1016/S1473-3099(03)00741-2.
57. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis.* 2003;3(3):148-155. doi:10.1016/S1473-3099(03)00545-0.
58. Guidelines BTS. BTS recommendations for assessing risk and for managing *Mycobacterium*

- tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax*. 2005;60(10):800-805. doi:10.1136/thx.2005.046797.
59. Keane J, Gershon S, Wise RP, Mirabile-levens E, Kasznica J, Schwiertman WD, Siegel JN BM. Tuberculosis Associated With Infliximab ,. *N Engl J Med*. 2001;345(15):1098-1104.
60. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis Rheum*. 2005;52(10):2968-2974. doi:10.1002/art.21382.
61. Mariette X, Baron G, Tubach F, et al. Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy. *Ann Rheum Dis*. 2012. doi:10.1136/annrheumdis-2011-200408.
62. Edwards A, Gao Y, Allan RN, et al. Corticosteroids and infliximab impair the performance of interferon- γ release assays used for diagnosis of latent tuberculosis. *Thorax*. 2017.
63. Rutledge TF, Boyd MF, Mazurek M, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm reports Morb Mortal Wkly Rep Recomm reports / Centers Dis Control*. 2010;59(RR-5):1-25. doi:rr5415a4 [pii].
64. Group IBD. Evidence-based consensus on opportunistic infections in inflammatory bowel disease. *Intest Res*. 2018;16(2):178-193.
65. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis*. 2014;8(6):443-468. doi:10.1016/j.crohns.2013.12.013.
66. Ziakas PD, Mylonakis E. 4 Months of Rifampin Compared with 9 Months of Isoniazid for the Management of Latent Tuberculosis Infection: A Meta-analysis and Cost-Effectiveness Study That Focuses on Compliance and Liver Toxicity. *Clin Infect Dis*. 2009.

doi:10.1086/647944.

67. Park S-J, Jo K-W, Yoo B, et al. Comparison of LTBI treatment regimens for patients receiving anti-tumour necrosis factor therapy. *Int J Tuberc Lung Dis Off J Int Union Against Tuberc Lung Dis*. 2015. doi:10.5588/ijtld.14.0554.
68. Vonkeman H, ten Napel C, Rasker H, van de Laar M. Disseminated primary varicella infection during infliximab treatment. *J Rheumatol*. 2004;31(12):2517-2518.
69. Kopylov U, Levin A, Mendelson E, et al. Prior varicella zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: Implications for serological testing and vaccination guidelines. *Aliment Pharmacol Ther*. 2012. doi:10.1111/j.1365-2036.2012.05150.x.
70. Reich J, Wasan SK, Farraye FA. Vaccination and Health Maintenance Issues to Consider in Patients With Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)*. 2017.
71. Cullen G, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012. doi:10.1002/ibd.22950.
72. Gupta G, Lautenbach E, Lewis JD. Incidence and Risk Factors for Herpes Zoster Among Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2006. doi:10.1016/j.cgh.2006.09.019.
73. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013. doi:10.1111/apt.12182.
74. Department of Health. *Chapter 34: Varicella.*; 2012.
75. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention , diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis*. 2014;8(6):443-468. doi:10.1016/j.crohns.2013.12.013.

76. Guidotti LG, Ishikawa T, Hobbs M V., Matzke B, Schreiber R, Chisari F V. Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity*. 1996;4(1):25-36. doi:10.1016/S1074-7613(00)80295-2.
77. Wendling D, Auge B, Bettinger D, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthritis. *Ann Rheum Dis*. 2005;64(5):788-789. doi:10.1136/ard.2004.031187.
78. Charpin C, Guis S, Colson P, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. *Arthritis Res Ther*. 2009;11(6):R179. doi:10.1186/ar2868.
79. Doubrawa E, Augusto R, Ricca DM, et al. Use of infliximab in a patient with rheumatoid arthritis and chronic hepatitis B. 2012;52(4):50-52.
80. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut*. 2004;53(9):1363-1365. doi:10.1136/gut.2004.040675.
81. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. *Clin Mol Hepatol*. 2016. doi:10.3350/cmh.2016.0024.
82. Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2010;31(1):20-34. doi:10.1111/j.1365-2036.2009.04112.x.
83. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. *Ann Rheum Dis*. 2004;63 Suppl 2:ii18-ii24. doi:10.1136/ard.2004.028209.
84. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. *J Gastroenterol Hepatol*.

- 2006;21(9):1366-1371. doi:10.1111/j.1440-1746.2006.04559.x.
85. Fauci AS. Host factors and the pathogenesis of HIV-induced disease. *Nature*. 1996;384(6609):529-534. doi:10.1038/384529a0.
86. Poli G. Laureate ESCI award for excellence in clinical science 1999. Cytokines and the human immunodeficiency virus: From bench to bedside. *Eur J Clin Invest*. 1999;29(8):723-732. doi:10.1046/j.1365-2362.1999.00525.x.
87. T. H. Ho, R. Fausel, J. Torres, J. J. Yang, T. H. Swartz, J. A. Aberg, J.-F. Colombel SM. The effect of concurrent HIV-1 infection on the management of patients with inflammatory bowel disease. *J Crohns Colitis*. 2016;(supplement):S330.
88. Abreu C, Magro F, Vilas-Boas F, Lopes S, Macedo G, Sarmento A. Listeria infection in patients on anti-TNF treatment: report of two cases and review of the literature. *J Crohns Colitis*. 2013;7(2):175-182. doi:10.1016/j.crohns.2012.04.018.
89. Toruner M, Loftus E V., Harmsen WS, et al. Risk Factors for Opportunistic Infections in Patients With Inflammatory Bowel Disease. *Gastroenterology*. 2008;134(4):929-936. doi:10.1053/j.gastro.2008.01.012.
90. Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. *J Clin Rheumatol*. 2007;13(2):79-80. doi:10.1097/01.rhu.0000260411.75599.39.
91. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis*. 2008;67(5):710-712. doi:10.1136/ard.2007.081513.
92. George A. Stamatiades, Petros Ioannou GP and CT. Fungal infections in patients with inflammatory bowel disease: A systematic review. *Mycoses*. 2018;June(61(6)):366-376. doi:10.1111/myc.12753.

93. Roilides E, Dimitriadou-Georgiadou a, Sein T, Kaditsoglou I, Walsh TJ. Tumor necrosis factor alpha enhances antifungal activities of polymorphonuclear and mononuclear phagocytes against *Aspergillus fumigatus*. *Infect Immun*. 1998;66(12):5999-6003.
94. Warris A, Bjørneklett A GP. Invasive Pulmonary Aspergillosis Associated with Infliximab Therapy. *N Engl J Med*. 2001;344(14)(Apr 5):1099-1100.
95. Manz M, Beglinger C, Vavricka SR. Fatal invasive pulmonary aspergillosis associated with adalimumab therapy. *Gut*. 2009;58(1):149. doi:10.1136/gut.2008.161638.
96. Lee J-H, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum*. 2002;46(10):2565-2570. doi:10.1002/art.10583.
97. FDA. Drugs Information for Healthcare Professionals : Cimzia (certolizumab pegol), Enbrel (etanercept),. 2008:1-3.
98. D'Ovidio V, Vernia P, Gentile G, et al. Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFalpha therapy. *J Clin Virol*. 2008;43(2):180-183. doi:10.1016/j.jcv.2008.06.002.
99. Van Assche G, Vermeire S, Rutgeerts P. Management of acute severe ulcerative colitis. *Gut*. 2011;60(1):130-133. doi:10.1136/gut.2009.192765.
100. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. *J Crohn's Colitis*. 2013;7(1):1-33. doi:10.1016/j.crohns.2012.09.005.
101. Kopylov U, Sasson G, Geyshis B, et al. Cytomegalovirus positive ulcerative colitis: A single center experience and literature review. *World J Gastrointest Pathophysiol*. 2013;4(1):18-23. doi:10.4291/wjgp.v4.i1.18.
102. Kopylov U, Papamichael K, Katsanos K, et al. Impact of Infliximab and Cyclosporine on the

- Risk of Colectomy in Hospitalized Patients with Ulcerative Colitis Complicated by Cytomegalovirus - A Multicenter Retrospective Study. *Inflamm Bowel Dis*. 2017. doi:10.1097/MIB.0000000000001160.
103. Pillet S, Jarlot C, Courault M, et al. Infliximab does not worsen outcomes during flare-ups associated with cytomegalovirus infection in patients with ulcerative colitis. *Inflamm Bowel Dis*. 2015. doi:10.1097/MIB.0000000000000412.
104. Cotter TG, Gathaiya N, Catania J, et al. Low Risk of Pneumonia From Pneumocystis jirovecii Infection in Patients With Inflammatory Bowel Disease Receiving Immune Suppression. *Clin Gastroenterol Hepatol*. 2017. doi:10.1016/j.cgh.2016.11.037.
105. Kaur N, Mahl TC. Pneumocystis jirovecii (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci*. 2007;52(6):1481-1484. doi:10.1007/s10620-006-9250-x.
106. Sánchez-Tembleque MD, Corella C, Pérez-Calle JL. Vaccines and recommendations for their use in inflammatory bowel disease. *World J Gastroenterol*. 2013;19(9):1354-1358. doi:10.3748/wjg.v19.i9.1354.
107. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: Twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum*. 2002;46(12):3151-3158. doi:10.1002/art.10679.
108. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol*. 2005;32(11):2130-2135.
109. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295(19):2275-2285. doi:10.1001/jama.295.19.2275.
110. Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with

- tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf.* 2011;20(2):119-130. doi:10.1002/pds.2046.
111. Caspersen S, Elkjaer M, Riis L, et al. Infliximab for Inflammatory Bowel Disease in Denmark 1999-2005: Clinical Outcome and Follow-Up Evaluation of Malignancy and Mortality. *Clin Gastroenterol Hepatol.* 2008;6(11):1212-1217. doi:10.1016/j.cgh.2008.05.010.
112. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious Infections and Mortality in Association With Therapies for Crohn's Disease: TREAT Registry. *Clin Gastroenterol Hepatol.* 2006;4(5):621-630. doi:10.1016/j.cgh.2006.03.002.
113. Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. *Am J Gastroenterol.* 2014;109(2):212-223. doi:10.1038/ajg.2013.441.
114. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009. doi:10.1016/S0140-6736(09)61302-7.
115. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology.* 2011;141(5):1621-1628. doi:10.1053/j.gastro.2011.06.050.
116. Long MD, Herfarth HH, Pipkin C, Porter CQ, Sandler RS, Kappelman M. Increased Risk for Non-Melanoma Skin Cancer in Patients with Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2010;8(3):268-274. doi:10.1016/j.cgh.2009.11.024.Increased.
117. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology.* 2012. doi:10.1053/j.gastro.2012.05.004.

118. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA*. 2017;318(17):1679. doi:10.1001/jama.2017.16071.
119. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohn's Colitis*. 2010;4(5):511-522. doi:10.1016/j.crohns.2010.05.006.
120. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohn's Colitis*. 2010. doi:10.1016/j.crohns.2010.05.006.
121. Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(12):2146-2153. doi:10.1038/ajg.2011.283.
122. Siegel C a., Marden SM, Persing SM, Larson RJ, Sands BE. Risk of Lymphoma Associated With Combination Anti-Tumor Necrosis Factor and Immunomodulator Therapy for the Treatment of Crohn's Disease: A Meta-Analysis. *Clin Gastroenterol Hepatol*. 2009;7(8):874-881. doi:10.1016/j.cgh.2009.01.004.
123. Axelrad J, Bernheim O, Colombel JF, et al. Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol*. 2016. doi:10.1016/j.cgh.2015.07.037.
124. Shelton E, Laharie D, Scott FI, et al. Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. *Gastroenterology*. 2016. doi:10.1053/j.gastro.2016.03.037.
125. Annese V, Beaugerie L, Egan L, et al. European evidence-based consensus: Inflammatory bowel disease and malignancies. *J Crohn's Colitis*. 2015. doi:10.1093/ecco-jcc/jjv141.

For Peer Review